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SURGICAL TREATMENT OF SYPHILITIC PRIMARY ATROPHY OF THE OPTIC NERVES (SYPHILITIC OPTOCHIASMATIC ARACHNOIDITIS)

A Clinicoanatomic Study*

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OF LATE a number of publications have appeared on the surgical treatment of syphilitic primary atrophy of the optic nerves.[1] Neurosurgical intervention in treatment of this condition is based on the recently advanced theory that syphilitic arachnoiditis, involving the optic nerves, produces atrophy of the nerves. The purpose of the operation is to free the optic nerves of the adhesions believed responsible for pressure and constriction, which is followed by atrophy of the nerves.

In the past other hypotheses of the pathogenesis of primary syphilitic optic nerve atrophy, formerly called tabetic optic nerve atrophy, have been advanced. The earliest theory placed the essential lesion in the ganglion cells of the retina. Some investigators expressed the belief that the atrophy originated as a primary degeneration of the nerve fibers. The "retinal theory" was disproved by the work of Léri,[2] who, on the basis of the histologic examination of a large anatomic material, expressed the view that the primary lesion of tabetic atrophy of the optic nerve consists in an interstitial neuritis. Similar conclusions were reached by

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1. (*a*) Vincent, C.; Jeandelize, and Bretagne: Atrophie optique tabétique et neuro-chirurgie, Bull. Soc. d'opht. de Paris **49**:245, 1937. (*b*) Vail, D.: Syphilitic Opticochiasmatic Arachnoiditis, Am. J. Ophth. **22**:505, 1939. (*c*) Hausman, L.: Blindness Due to Syphilitic Arachnoiditis of the Optic Nerves and Chiasm: Restoration of Vision Following Surgical Intervention, Tr. Am. Neurol. A. **65**: 181, 1939; (*d*) Syphilitic Atrophy of the Optic Nerve and Papilledema Due to Optochiasmal Arachnoiditis: Indications for Surgical Intervention, Arch. Ophth. **23**:1107 (May) 1940; (*e*) The Surgical Treatment of Syphilitic Optic Atrophy Due to Chiasmal Arachnoiditis, Am. J. Ophth. **24**:119, 1941. (*f*) Schaub, C. F.: Surgical Treatment of Syphilitic Optic Atrophy (Syphilitic Optico-Chiasmatic Arachnoiditis), Dis. Eye, Ear, Nose & Throat **1**:326, 1941.

2. Lérie, A.: Étude de la rétine dans l'amaurose tabétique, Nouv. iconog. de la Salpêtrière **17**:304, 1904; Étude du nerf optique dans l'amaurose tabétique, ibid. **17**:358, 1904.

Stargardt,[3] Richter [4] and Bruetsch,[5] who observed the chief site of the inflammatory process within the intracranial portion of the optic nerves and in the chiasm.

EVOLUTION OF THE THEORY THAT OPTOCHIASMATIC ARACHNOIDITIS PRODUCES ATROPHY OF THE OPTIC NERVES

The clinical importance of an arachnoiditis localized at the base of the brain was recognized by Horrax.[6] He described a number of cases from Cushing's clinic in which rapid loss of vision, accompanied with signs of intracranial pressure, such as headache, vomiting and choked disk, subsided after surgical intervention. One of the typical cases of his series was that of a 13 year old boy, whose illness began with generalized headaches, followed by blurring of vision and diplopia. One month later the child was nearly blind. Cushing explored the cerebellum, and an enlarged posterior cistern with a thickened arachnoidal wall was disclosed. The arachnoid was incised, releasing a large amount of cerebrospinal fluid. After the operation there was an astounding return of vision, accompanying the rapid subsidence of the papilledema. In this case failing vision was caused by arachnoiditis localized over the cerebellum and producing a rather sudden obstruction of the free flow of cerebrospinal fluid, resulting in pronounced intracranial hypertension. The arachnoiditis, through overextension of the cistern over the cerebellum, brought about by sudden blocking of intraventricular drainage, produced symptoms similar to those observed with tumors of the posterior fossa. Arachnoiditis in this region is often clinically indistinguishable from tumors of the cerebellum and has been classified by some authors as "pseudotumor." [7] In cases of arachnoiditis in the cerebellar area atrophy of the optic nerve is produced by the mere increase in intracranial pressure, and not by direct mechanical constriction of the optic nerves. This condition requires surgical relief, for the same reasons that tumors do, if vision is to be preserved. The disappearance of the symptoms depends on the reconstruction of a normal mechanism for circulation of the cerebrospinal fluid. As to the etiologic factors in this type of arachnoiditis, nothing definite can be

3. Stargardt: Ueber die Ursachen des Sehnervenschwundes bei der Tabes und der progressiven Paralyse, Arch. f. Psychiat. **51**:711, 1913.

4. Richter, H.: Zur Histogenese der Tabes, Ztschr. f. d. ges. Neurol. u. Psychiat. **67**:1, 1921.

5. Bruetsch, W. L.: Malaria Therapy in Syphilitic Primary Optic Atrophy, J.A.M.A. **130**:14 (Jan. 5) 1946.

6. Horrax, G.: Generalized Cisternal Arachnoiditis Simulating Cerebellar Tumor: Its Surgical Treatment and End-Results, Arch. Surg. **9**:95 (July) 1924.

7. Frazier, C. H.: Cerebral Pseudotumors, Arch. Neurol. & Psychiat. **24**: 1117 (Dec.) 1930.

said, except in the cases in which it follows otitis media. In none of Horrax's [6] cases was there any evidence of syphilis.

There is a second group of cases in which arachnoiditis, localized over the anterior, or optochiasmatic, cistern, is said to produce atrophy of the optic nerves. The absence of choked disks and of other signs of intracranial pressure in the presence of failing vision sets these cases distinctly apart from the first group. It is this type of cases, with failing vision, which in the past decade has attracted the attention of neurosurgeons and has resulted in an outpouring of papers on the surgical treatment of optic nerve atrophy.

Balado,[8] in 1929, operated in such a case with the hope of relieving the stricture of the optic nerves caused by the arachnoidal adhesions. The history of Balado's famous case is briefly summarized.

A man aged 35 experienced loss of vision within six months so that he could differentiate only between light and darkness. Perimetric examination showed advanced constriction of the visual fields. There was gray atrophy of the optic disks. No other neurologic abnormalities were noted. Intelligence was not impaired. The Wassermann reactions of the blood and the cerebrospinal fluid were negative. Operation revealed that the arachnoid around the optic nerves was thickened, embedding in a newly formed membrane the left optic nerve. The thickened arachnoid around this nerve was opened, and a thinned, atrophic nerve came into view. In the months following the operation vision improved to such a degree that the patient could earn a living at a simple job, but not at his former occupation, which was that of a tinsmith. Although a piece of the surgically removed arachnoidal tissue was examined histologically, showing simple fibrosis, the cause of the optochiasmatic arachnoiditis could not be determined. Surgical removal of the thickened arachnoid, however, brought only partial relief, the arachnoidal thickening apparently not being the sole cause of the atrophy of the visual nerve fibers.

Balado's operation initiated the period of surgical intervention for relief of optic nerve atrophy. Since then, attention has been focused on the occurrence of such cases. Heuer and Vail [9] stressed that primary optic nerve atrophy alone, in the absence of any other neurologic manifestations, may be an indication for operation directed toward the relief of pressure on the optic chiasm.

Vincent, in France, contributed repeatedly to knowledge of this condition, his work culminating in a monograph by his associates,[10] in which a comprehensive survey of optochiasmatic arachnoiditis is presented.

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8. Balado, M., and Satanowsky, P.: Tratamiento quirúrgico de la atrofia de la papila, Arch. argent. de neurol. **4**:71, 1929.

9. Heuer, G. J., and Vail, D. T.: Chronic Cisternal Arachnoiditis Producing Symptoms of Involvement of the Optic Nerves and Chiasm: Pathology and Results of Operative Treatment in Four Cases, Arch. Ophth. **5**:334 (March) 1931.

10. Bollack, J.; David, M., and Puech, P.: Les arachnoïdites opto-chiasmatiques. Étude ophtalmologique et neuro-chirurgicale, Paris, Masson & Cie, 1937.

The etiologic factor in optochiasmatic arachnoiditis remains obscure in most cases,[11] except in those which follow otitis media and a syphilitic infection. In most other cases with symptoms of optochiasmatic arachnoiditis there is apparently a process within the optic chiasm, either inflammatory or demyelinating, involving the nerve fibers and the arachnoid at the same time.

SYPHILITIC OPTOCHIASMATIC ARACHNOIDITIS

In the discussion of optochiasmatic arachnoiditis syphilis has only of late received consideration. In most cases in which an exploration of the chiasm was performed the process was of nonsyphilitic origin. Only since 1934 has syphilis been given the prominent role which it deserves in the causation of arachnoiditis, although it occurs mostly in asymptomatic form.[11] Subsequently, from a neurosurgical standpoint, its importance has been overemphasized, for the idea has been accepted widely that syphilitic arachnoiditis, involving the optic nerves, is responsible for syphilitic primary optic nerve atrophy.

Probably the first to operate for syphilitic primary optic nerve atrophy was Cushing.[12] In 1930, in a series of other cases, he reported the history of a patient aged 39 with progressive failure of vision of three years' standing, bitemporal field defects and large central scotomas. The optic disks showed grayish atrophy. Vision was 2/200 in the left eye and 20/50 in the right eye. The patient had a history of possible congenital syphilitic infection, for which he had not been treated. The Wassermann test of the blood gave a negative reaction, but the lumbar spinal fluid showed a trace of globulin, 7 cells per cubic millimeter and slightly positive Wassermann and Kahn reactions. Except for the ophthalmologic findings, the physical examination was wholly without significance. The patient was first placed under routine antisyphilitic treatment, but vision kept on failing. It was then thought that the condition was due to a tumor, and operation was advised. Exploration disclosed that the chiasm was embedded in a distinctly thickened and grayish arachnoid, containing a great excess of fluid. The patient made a perfect recovery from the operation, but there was no improvement in vision.

Cushing, with his keen judgment, recognized at once the reason for the lack of visual improvement in this case. The cause, as he explained it, may lie in the fact that the same process which caused the thickening of the pia-arachnoid likewise affected and permanently damaged the optic nerves. His assumption proved to be correct, as will be shown in the present study, which was directed toward the solution of this question.

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11. Bruetsch, W. L.: The Etiology of Optochiasmatic Arachnoiditis, Arch. Neurol. & Psychiat., to be published.

12. Cushing, H.: The Chiasmal Syndrome of Primary Optic Atrophy and Bitemporal Field Defects in Adults with a Normal Sella Turcica, Arch. Ophth. **3**:505 (May); 704 (June) 1930.

REPORT OF CASES

CASE 1.—*Primary syphilitic optic nerve atrophy occurring in a patient with tabes dorsalis; syphilitic optochiasmatic arachnoiditis as a possible cause of atrophy of the optic nerves.*

History.—The patient had had a chancre at the age of 18. Twenty years later he experienced the first shooting pains. During the next year he became aware of obscuration of vision. This led him to consult a physician, who gave him five injections of neoarsphenamine. This was the first time that he received any treatment for syphilis. Vision decreased steadily, and within one year he was completely blind. Gastric crises then developed. Several years later he began to have difficulty in walking, and at the age of 57 he had completely lost control of both lower extremities.

Fig. 1 (case 1).—Primary syphilitic atrophy of the optic nerves in a tabetic patient. Arachnoidal bands (syphilitic optochiasmatic arachnoiditis) extend from the pons and insert on both optic nerves in front of the chiasm.

Physical Examination.—The patient, aged 57, was totally blind. He could not perceive even a very bright light with either eye. Both optic disks were chalky white. The other neurologic signs were typical of tabes dorsalis. Memory was good, and there was no psychosis. The Wassermann, Kahn and Kline reactions of the blood were negative. The Wassermann reaction of the spinal fluid was positive. The cell count of the fluid was 3 cells per cubic millimeter, and the Ross-Jones and Pandy test gave weakly positive reactions. The colloidal gold curve was 0123321000.

The patient was given a course of malaria therapy, without improvement in sight or gait.

He died three months after admission to the hospital, of tuberculous spondylitis and pulmonary tuberculosis.

Postmortem Observations.—Firm arachnoidal adhesions originated in the middle portion of the pons and inserted on both optic nerves, immediately in front of the chiasm (fig. 1). Both third nerves emerged outside the adhesions. The thickened arachnoidal bands pulled the optic nerves and the optic chiasm backward, suggesting that during life traction was exerted on both nerves. The volume of the optic nerves was reduced to about one-half or less that of the normal nerve. Atrophy of the left optic nerve was even greater. At the site of insertion of the arachnoidal band on the left optic nerve there occurred a kink. Here the optic nerve fibers had almost entirely vanished.

The capsular surface of the hypophysis was thickened, giving the impression that at one time an intense inflammatory process had taken place about the optic chiasm and the hypophysis.

Fig. 2 (case 1).—Thickened optochiasmatic arachnoid passing over the atrophic optic nerve. Hematoxylin-eosin stain; × 50.

Histologic Examination.—Examination of the arachnoidal adhesions about the chiasm revealed a thickened membrane, consisting of several rows of proliferated arachnoidal cells. Next occurred an increased number of fibroblasts, which had produced a thickened layer of connective tissue (fig. 2). There were no round cell infiltrations or vessels showing syphilitic endarteritis. No spirochetes were observed in the thickened optochiasmatic arachnoid.

Both optic nerves, the optic chiasm and the optic tracts showed complete demyelination (atrophy). In some portions of the pia of the intracranial portion of the optic nerves a few scattered round cells were present. In the trabecular connective tissue of the interior of the intracranial portion of the optic nerves 1 plasma cell was noted in every third oil immersion field. Treponema pallidum was not identified in the optic nerves.

In the pia of the floor of the third ventricle and in other areas at the base of the brain plasma cells were arranged in single file. No such infiltration of plasma cells was present in the meninges over the upper aspect of the brain. The cerebral cortex was free of perivascular infiltrations, i.e., of changes characteristic of dementia paralytica.

The posterior columns of the spinal cord showed degeneration, characteristic of tabes.

Comment.—When I saw the base of this brain in 1932, I was convinced that the "tabetic optic nerve atrophy" in this case was the result of arachnoidal adhesions and that blindness could have been prevented by surgical intervention. I had this case in mind when I recommended surgical treatment for optic nerve atrophy in the discussion on the paper by Moore and Woods,[13] read before the Association of American Physicians in 1938. I did not publish the case because I wanted to collect other instances of syphilitic atrophy of the optic nerve. I began to accumulate anatomic material, not only of syphilitic atrophy of the optic nerves but also of atrophies caused by such conditions as brain tumor, multiple sclerosis and Schilder's disease. To form a sound judgment on the mechanism of degeneration of the nerve fibers in cases of optic nerve atrophy, which varies with the etiologic factor involved, it was necessary to examine histologically a large material of atrophies of the optic nerve of various causes.

Today I am no longer certain that the arachnoidal adhesions were the sole cause of the atrophy of the optic nerves in the case just described. Two reasons changed my mind. First, the intracranial portion of the optic nerves showed complete demyelination. If demyelination had been due to traction or pressure alone, i. e., to mechanical effects, areas with normal nerve fibers would have been left. Second, in the pia at the base of the brain there was a mild degree of plasma cell infiltration, indicating that basically the atrophy in this case had its origin in chronic basilar syphilitic meningitis, as it has in other instances of primary syphilitic atrophy of the optic nerves. In the intracranial portion of the optic nerves, in the chiasm and even more so within the optic tracts an occasional plasma cell was observed. This observation, however, cannot be given too much weight in the argument, because a few scattered plasma cells and lymphocytes are occasionally present within the optic nerves, the chiasm and the optic tracts of neurosyphilitic patients who do not have optic nerve atrophy. Furthermore, seventeen years had passed since the patient had become blind. It is obvious that during this period the degree of plasma cell infiltration at the base of the brain and within the optic nerves had undergone a reduction, adding to the difficulties of correct interpretation of the histologic observations.

13. Moore, J. E.; Woods, A. C.; Hopkins, H. H., and Sloan, L. L.: The Treatment of Syphilitic Primary Optic Atrophy, J.A.M.A. **111**:385 (July 30) 1938.

CASE 2.—*Development of atrophy of the optic nerves and bilateral ptosis in a patient with dementia paralytica four years after malarial therapy, in spite of rapid improvement in the spinal fluid. Optic nerve atrophy and involvement of the cranial nerves were assumed to be caused by syphilitic optochiasmatic arachnoiditis. The poor health of the patient prohibited surgical intervention. Necropsy revealed the striking absence of arachnoidal adhesions in the chiasmic region.*

History.—A woman aged 47 was admitted on July 26, 1928, with clinical and serologic signs of dementia paralytica. There were no complaints of failing vision. She was given a course of tertian malaria therapy, experiencing nine elevations of temperature, ranging from 101 to 104 F. After malarial therapy the acute mental symptoms of dementia paralytica subsided, but there was slowly progressing mental deterioration. For about two years after malarial therapy there was no obvious indication that her eyesight was failing. Then, in 1930, it was noted that she had difficulty in getting about the ward. At the same time, bilateral ptosis and paralysis of the left sixth nerve developed (fig. 3). Within one year, however, the ptosis improved considerably. At the end of 1932 vision had become reduced to a point at which the patient could perceive only strong light before her eyes. Owing to the deteriorated mental stage, examination of the visual fields was always unsatisfactory.

Fig. 3 (case 2).—Face of the patient with primary syphilitic atrophy of the optic nerves, accompanied with involvement of the third and sixth cranial nerves (ptosis and internal strabismus of the left eye). See figure 4, which shows the base of the brain of this patient.

Strikingly, the rapid loss of vision became noticeable during a time when there was pronounced improvement in the spinal fluid. In the two years following malarial therapy, the findings in the spinal fluid indicative of dementia paralytica remained unchanged except for the cell count. In the next three years, from 1930 to 1933, there was a complete return to normal of all reactions, including the Wassermann reaction, the cell count, the total protein content and the colloidal gold reaction.

In the succeeding years the patient became bedfast; sacral ulcers developed, and she died in 1940, of pyelonephritis.

Postmortem Observations.—Except for a few delicate strands of arachnoid passing over the right optic nerve, there were no arachnoidal adhesions in the optochiasmatic region (fig. 4). About the exit of both third nerves the pia-arachnoid revealed moderate thickening. The optic nerves had a grayish appearance and were reduced in size. Both third nerves were atrophied, having less than one-half the volume of a normal oculomotor nerve.

Histologic Examination.—There was complete gray atrophy (demyelination) of the optic nerves, optic chiasm (fig. 5) and optic tracts, giving the impression of "primary parenchymatous degeneration" of the nerve fibers. However, careful search revealed slight residual inflammatory changes in the form of scattered

foci of plasma cells and lymphocytes in isolated areas of the periphery of the optic nerves and chiasm (fig. 6). The visual pathways were examined for T. pallidum, but no organisms were seen. In the interior of the intracranial portion of the optic nerves and within the chiasm, about small vessels, from 2 to 5 plasma cells were noted in some oil immersion fields, while other fields were free of such

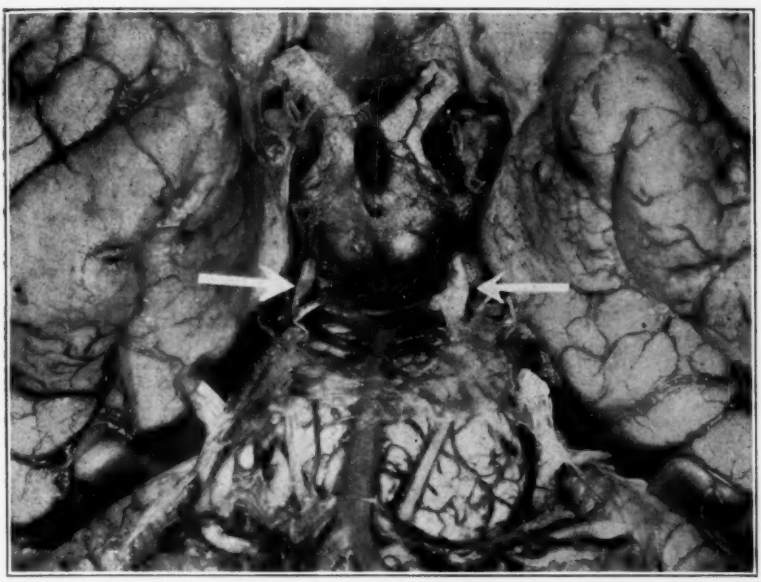

Fig. 4 (case 2).—Base of the brain of a patient with syphilitic atrophy of the optic nerves, revealing complete absence of optochiasmatic adhesions. Arrows point to the atrophied third nerves.

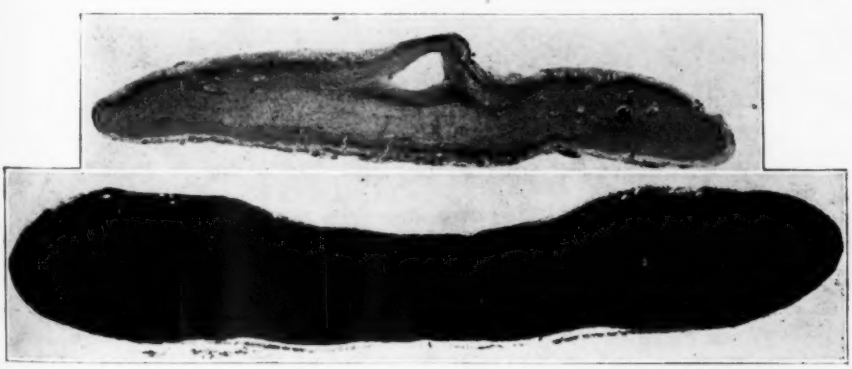

Fig. 5 (case 2).—Complete gray atrophy of the optic chiasm; Weil stain for myelin sheaths; × 7. The lower picture represents a normal optic chiasm, stained with the same stain and photographed with the same magnification for comparison.

cells. There were also enlarged perivascular spaces, although now empty of round cells, suggesting that at one time the exudative process had been much more intense.

In the orbital convolutions and over the pons the pia-arachnoid was practically normal, and only on intensive search could a few isolated round cells be detected. In other words, there was more round cell infiltration in the pia of the intracranial portion of the optic nerves than in other areas of the base of the brain.

Third Nerves: The pia of the third nerves was normal, but in the interior of the nerves plasma cells were more frequent than within the optic nerves. Some of the nerve fibers were partially demyelinated. The loss of myelin was more pronounced in the right than in the left third nerve. The ganglion cells of the nuclei of the third nerves were normal.

In the cerebral cortex the perivascular infiltrations had completely receded, leaving no trace of dementia paralytica evident even to the experienced observer.

The posterior columns of the cord showed a slight degree of degeneration of the tabetic type.

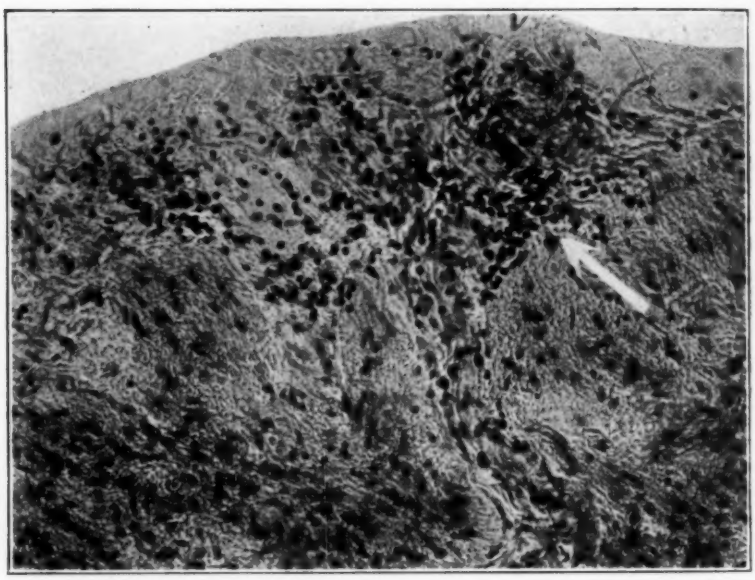

Fig. 6 (case 2).—Residual focus with plasma cells and lymphocytes in the pia of the intracranial portion of the atrophied optic nerve, persisting in spite of an entirely normal spinal fluid. Toluidine blue stain; × 225.

Comment.—In this case atrophy of the optic nerve developed slowly in the years following malarial therapy, and at a time when the spinal fluid findings were returning to normal. It was argued that contracting arachnoidal adhesions at the chiasm were the cause of the atrophy of the optic nerves. This belief was strengthened by the appearance of changes in the third and sixth cranial nerves, which were thought to be caused by the same arachnoidal adhesions. Exploration of the chiasm was considered, but the patient's poor state of health prohibited surgical intervention. At autopsy, the complete absence of arachnoidal adhesions at the base of the brain came as a surprise. Prior to death

much weight was given to Hausman's [14] statement that the diagnosis of syphilitic chiasmatic arachnoiditis should be considered when, in addition to atrophy of the optic nerves, there is involvement of other cranial nerves. This assertion is logical, for syphilitic arachnoiditis is usually not confined to the chiasm, but involves the entire base of the brain.

How, then, can one explain the occurrence of optic nerve atrophy and ptosis in the presence of an interpeduncular space entirely free of arachnoidal adhesions, and developing after an otherwise successful course of malarial therapy, as evidenced by improvement in the spinal fluid? Microscopic examination furnished the clue. The atrophy of the optic nerves in this case finds its explanation in the now definitely established theory that degeneration of the nerves occurs as the result of an inflammatory process within the nerves and the chiasm.

Therapeutic malaria cleared up the inflammatory process in the cerebral cortex but did not influence materially the round cell infiltration at the periphery of and within the optic nerves. There the inflammation continued, advancing slowly in the course of several years from the periphery toward the center of the nerves. That this sequence of events had taken place was substantiated by the observation that at the periphery of the optic nerves as well as within the septal connective tissue plasma cells could still be seen. In addition, in the interior of the chiasm were vessels surrounded with enlarged perivascular spaces, giving evidence that at one time rather heavy perivascular infiltrations were present.

An important point of clinical interest is the circumstance that all tests of the spinal fluid, including the Wassermann test, cell count, determination of the total protein and colloidal gold test, gave entirely normal results for five years prior to death. Yet histologic examination revealed that a slight exudative process was still present (fig. 6). This brings out the hitherto unsuspected fact that in spite of a completely normal spinal fluid a mild inflammation may persist about and within the optic nerves.

The ptosis is explained on a similar basis, namely, persistence of interstitial neuritis of the third nerves, leading to demyelination. Later, the inflammatory phenomena subsided, with restoration of partial function. The excellent regenerative ability of the third nerves was demonstrated experimentally in chimpanzees, in which functional recovery in ocular muscles took place after section of the oculomotor nerve.[15]

14. Hausman, L.: Relation of Syphilitic Optic Atrophy and Papilledema to Adhesions at the Chiasm: Indications for and Results of Surgical Treatment, Arch. Neurol. & Psychiat. **43**:1034 (May) 1940.

15. Bender, M. B., and Fulton, J. F.: Functional Recovery in Ocular Muscles of a Chimpanzee After Section of Oculomotor Nerve, J. Neurophysiol. **1**:144, 1938.

CASE 3.—*Isolated syphilitic primary atrophy of the optic nerves associated with involvement of the third and sixth cranial nerves, followed by development of dementia paralytica of tabetic type. Autopsy revealed syphilitic arachnoiditis involving the optic nerves, the chiasm and the third and sixth nerves. Surgical removal of arachnoidal adhesions would have been without avail, because the thickened arachnoid passed harmlessly over the chiasm and the diffuse infiltration of plasma cells within the optic nerves and the chiasm would have persisted.*

History.—A man aged 50, while operating a punch card machine, noticed that his eyesight was failing. Within the next four and one-half years impairment of vision progressed to total blindness. Six months later he became forgetful and exhibited paranoid tendencies toward his family, necessitating commitment to an institution.

Physical Examination.—The patient was totally blind. He could not perceive a flashlight immediately before his eyes. Both lids drooped, and the left eye was turned inward (fig. 7). Both pupils were in mid-dilatation, of equal size, slightly irregular in outline, and fixed to light. Both optic disks had sharp outlines and were distinctly atrophic.

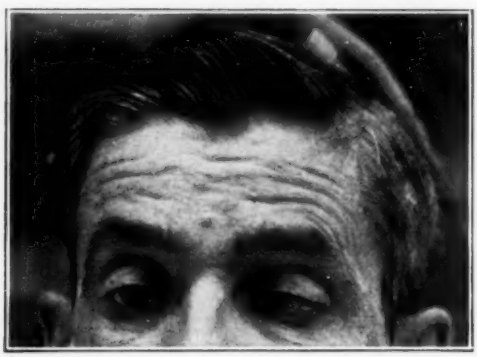

Fig. 7 (case 3).—Face of patient with primary syphilitic atrophy of the optic nerves, associated with partial ptosis and internal strabismus of the left eye (involvement of the third and sixth nerves), followed five years later by dementia paralytica of tabetic form. Figure 8 shows the optochiasmatic region of this patient.

Hearing was diminished on the right side. The patellar reflex was absent bilaterally. The patient was unable to walk, and gait could not be tested. There was incontinence of urine. Mental deterioration was evident.

Examination of the lumbar cerebrospinal fluid showed a positive Wasssermann reaction, a trace of globulin, 17 cells per cubic millimeter and a colloidal gold curve of 4443321000. The Wassermann, Kahn and Kline reactions of the blood were positive.

The patient died eighteen months after admission, of bronchopneumonia.

Postmortem Examination.—On elevation of the frontal lobes of the brain, a thickened arachnoid was noted, which extended along both optic nerves to the optic foramens. The brain was carefully removed without disturbing the arachnoidal adhesions. Examination of the base of the brain revealed syphilitic arachnoiditis (fig. 8). The thickened arachnoid extended from the pons, embedded tightly both third nerves, surrounded the internal carotid arteries and continued to the optic chiasm. A thick arachnoidal band stretched over the right optic nerve and ter-

minated in front of the chiasm. There was no pressure indentation in the right optic nerve of the type that has been described and sketched by investigators of this subject.[16] Both optic nerves were somewhat reduced in size, but the diagnosis of atrophy of the nerves could not be made with certainty from the gross appearance of the nerves, which were of fairly good volume. The third nerves were definitely atrophied and emerged through the fibrosed arachnoid. The pia-arachnoid over the tip of both temporal lobes and over the anterior portion of the orbital region was transparent.

Microscopic Examination.—The myelin sheath preparations showed complete gray atrophy of both optic nerves, with no remaining normal nerve fibers (fig. 9). The atrophy was also complete in the chiasm and in the optic tracts. In the pia of the intracranial portion of both optic nerves there were round cell infiltrations, which in isolated places formed massive foci and penetrated toward the interior (fig. 10). Throughout the entire diameter of the intracranial portion of both optic

Fig. 8 (case 3).—Primary syphilitic atrophy of the optic nerves with syphilitic optochiasmatic arachnoiditis. The thickened arachnoid embraces both third nerves (arrows) and internal carotid arteries and continues over the chiasm to the orbital convolutions.

nerves there was moderate plasma cell infiltration, occurring mostly about small vessels and capillaries. The plasma cells were arranged in single file and could not be seen with low power magnification, such as that in figure 10. A similar, but more intense, inflammatory process prevailed about and within the chiasm, where plasma cells and lymphocytes were scattered everywhere. Sometimes in one oil immersion field as many as 10 plasma cells could be observed. In other words, in the optic nerves, in the chiasm and, to a lesser degree, in the optic tracts there was an interstitial neuritis. Spirochetes were not observed in the structures of the visual pathways.

16. Rea, R. L.: Neuro-Ophthalmology, St. Louis, C. V. Mosby Company, 1941, p. 591.

Optochiasmatic Arachnoid: At no place did the arachnoid have a constricting or pulling effect on the optic nerves, the chiasm or the third nerves. The thickened arachnoid was diffusely infiltrated in its entire width with lymphocytes and plasma cells.

There was a similar round cell infiltration in the pia of the stalk of the hypophysis, and even within the stalk plasma cells were present in diffuse fashion.

In the pia at the base of the brain, adjacent to the chiasm, round cell infiltration was slight, while, in contrast, in the pia of the chiasm the inflammatory process was much more intense. A few vessels at the base of the brain exhibited syphilitic panarteritis.

In the cortex of the orbital and temporal lobes and in the gray matter extending upward as far as the island of Reil there were slight perivascular infiltrations,

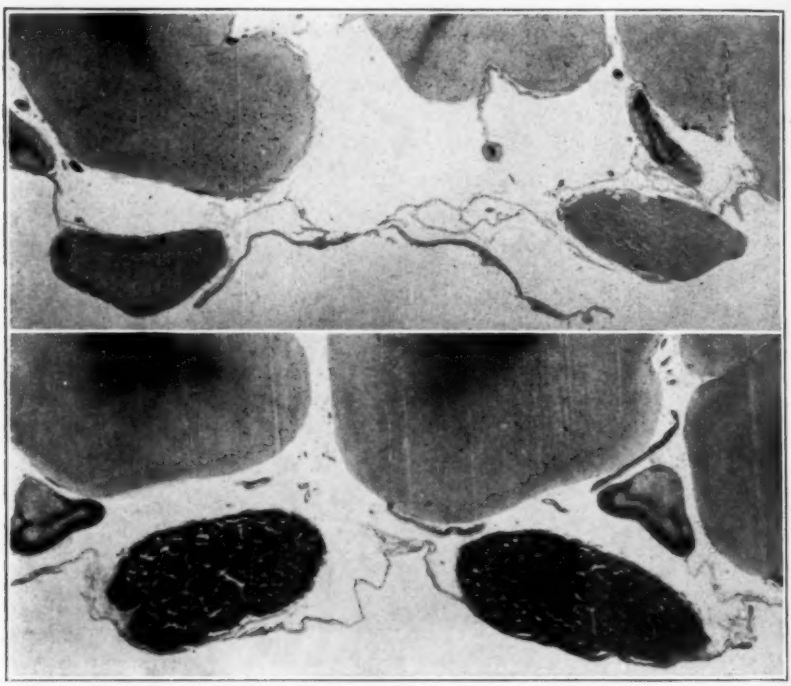

Fig. 9 (case 3).—Complete gray atrophy of both optic nerves. Note the arachnoid passing harmlessly over the optic nerves. Weil myelin sheath stain; × 5½. The lower picture shows normal optic nerves, stained with the same stain, for comparison.

but in the upper part of the brain the cortex was strikingly free of exudative changes.

Third Nerves: Around the periphery of the third nerves there was definite round cell infiltration. Everywhere in the interior of the third nerves were numerous plasma cells, averaging from 15 to 20 in one oil immersion field. The oculomotor nerves disclosed a considerable degree of demyelination. The arachnoid, which was diffusely infiltrated with round cells, passed over the third nerves without compressing the nerve structures. The nuclei of both third nerves were normal.

In the spinal cord was moderate degeneration of the posterior columns.

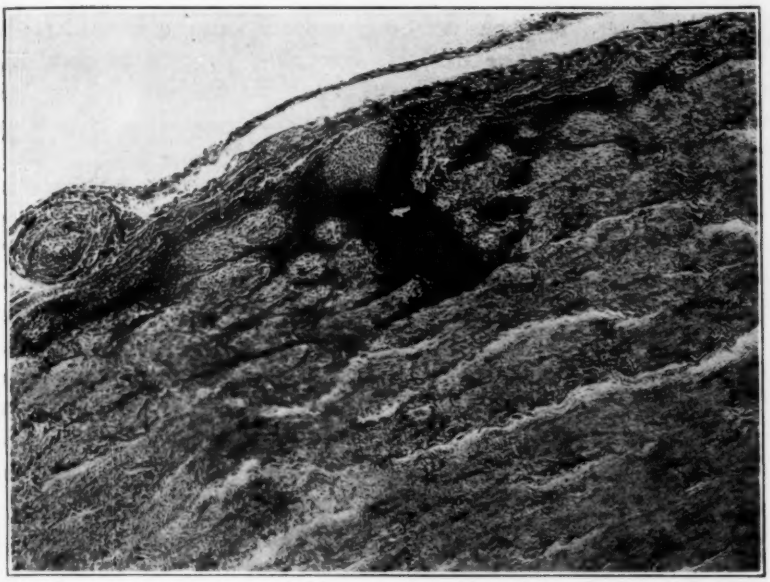

Fig. 10 (case 3).—Intracranial portion of the optic nerve with massive inflammatory focus penetrating from the margin toward the interior. Throughout the entire diameter of the optic nerve there is plasma cell infiltration, which cannot be seen with this low magnification. Toluidine blue stain; × 75.

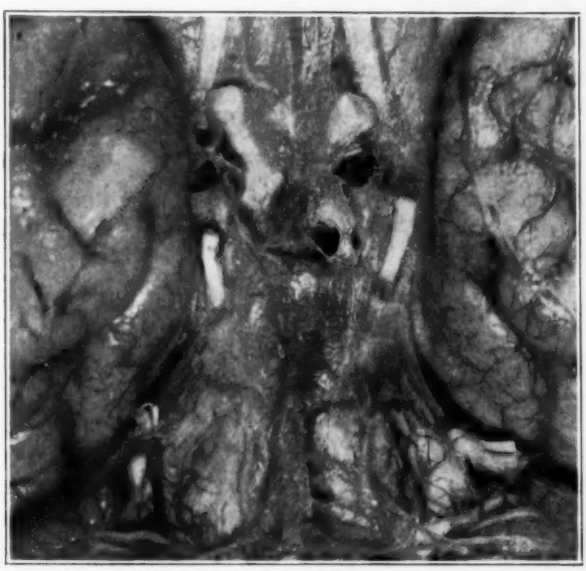

Fig. 11.—Asymptomatic, syphilitic optochiasmatic arachnoiditis without optic nerve atrophy.

Comment.—If at an earlier stage of the atrophy of the optic nerves in this case the chiasm had been explored, the surgeon would have noted thick arachnoidal adhesions. However, the surgical removal of the thickened optochiasmatic arachnoid would have been without benefit, for the inflammatory process within the optic nerves and chiasm would have continued.

The accompanying involvement of the third and sixth nerves had suggested that basilar arachnoiditis produced ptosis and internal strabismus as a result of mechanical pressure. The gross appearance of the base of the brain also seemed to substantiate this clinical interpretation. Microscopic examination corrected this impression, showing that the atrophy of both third nerves was the result of an interstitial neuritis. In summary, one may say that the same inflammatory process which had produced the atrophy of the optic nerves had caused the atrophy of the third nerves. The thickening of the arachnoid was only secondary to the existing basilar meningitis, and was of no essential consequence in the causation of the nerve atrophies.

COMMENT

In addition to the 3 cases reported in this paper, 9 other instances of syphilitic atrophy of the optic nerves formed the material of this study. In none of the cases, with the possible exception of case 1, was there any anatomic evidence that the arachnoidal adhesions, if they were present at all, were the cause of the atrophy of the optic nerves. In case 1, at the time of the gross inspection, it appeared that the arachnoidal fibrosis had exerted a pulling effect on the optic nerves, causing mechanical atrophy of the nerve fibers. Histologic examination, however, indicated that the atrophy of the optic nerves, as in all the other cases, was very likely the result of an interstitial neuritis. After the optic nerves had wasted and the fibrosed arachnoid had contracted, the arachnoidal bands pulled back the atrophied nerves and created a condition which at first sight was suggestive of a mechanical cause of the atrophy.

THE MECHANICAL THEORY OF OPTIC NERVE ATROPHY

What convinced me most that the optochiasmatic adhesions of syphilis are not the cause of optic nerve atrophy was a study of the effect of pressure which was exerted directly by tumors on the optic nerves. Contrary to common belief, the optic nerves are tough structures, which can withstand much pressure without undergoing generalized atrophy. The histologic picture of pressure atrophy of the optic nerves is entirely different from that of syphilitic atrophy of the nerves. In the case of optic nerve atrophy due to direct pressure one finds peripheral and other circumscribed areas of normal-staining nerve fibers, although the

optic nerves may have been reduced to ribbons. In the case of complete syphilitic optic nerve atrophy no normal nerve fibers are left, and the optic nerves may have retained a fairly good volume. If the atrophy associated with syphilis is not complete, the preserved tissue is usually situated in the center of the nerve, indicating that the interstitial neuritis, which progresses from the margin, has not yet reached the centrally located nerve fibers.

FREQUENCY OF OPTOCHIASMATIC ARACHNOIDITIS ASSOCIATED WITH SYPHILITIC PRIMARY ATROPHY OF THE OPTIC NERVES

In making explorations of the chiasm in cases of syphilitic atrophy of the optic nerves, some operators reported the consistent presence of arachnoidal adhesions, while others failed to observe pathologic arachnoidal bands. From these reports one gains the impression that neurosurgeons have little conception as to what is a normal and what is an abnormal arachnoid. Fine bands of arachnoid arising from the neighboring arteries and stretching over the optic nerves and chiasm are frequently present and are a normal variant of the chiasmatic cistern. Throughout the present study special attention was given to the state of the optochiasmatic arachnoid. Of 12 cases of syphilitic optic nerve atrophy the interpeduncular space was entirely free in 4, or 33 per cent. In 2 cases, or 17 per cent, there was slight arachnoidal thickening, which was not outside possible physiologic limitations. In the remaining 50 per cent there was increased thickening of the arachnoid, which permitted the diagnosis of syphilitic optochiasmatic arachnoiditis. In none of my cases had the arachnoid assumed the thickness shown in the 2 photographs illustrating nonsyphilitic arachnoiditis presented by Horrax.[6]

In a series of 100 cases of dementia paralytica without optic nerve atrophy there was a somewhat similar, but in one respect significantly different, percentage as to the presence or absence of thickening of the optochiasmatic arachnoid. In 27 per cent of the cases the base of the brain was free of arachnoidal adhesions. In 52 per cent the arachnoid was somewhat thickened, but was possibly still within normal limits. Only in 21 per cent was there unmistakable optochiasmatic arachnoidits. This figure is in contrast to the 50 per cent in cases of syphilitic optic nerve atrophy. This observation could be interpreted as indicating that in patients with optic nerve atrophy there is generally a higher degree of meningitis at the base of the brain than in neurosyphilitic patients without optic atrophy. This interpretation would accord well with the idea that optic nerve atrophy is the result of basilar syphilitic meningitis. However, the decisive factor in the genesis of optic nerve atrophy is not the mechanical effect of arachnoidal thickening; rather, it is the inflammatory process, and whether this process

penetrates into the optic nerves or the exudative phenomenon remains confined to the pia and arachnoid. The importance of this factor is illustrated by the cases of neurosyphilis without optic atrophy. In figure 11 one sees arachnoidal adhesions which are as thick as those in cases of optic nerve atrophy. Yet in this case there was no atrophy of the optic nerves, for the round cells, which were present in the pia and arachnoid, had not invaded the interior of the optic nerves. It is significant that both Léri [2] and Stargardt,[3] in their excellent anatomic studies dealing with syphilitic atrophy, noted the arachnoidal bands in the optochiasmatic region, but did not attribute to them any particular significance in the genesis of the atrophy of the optic nerves.

RESULT OF OPERATIONS

Surgical intervention in cases of syphilitic optic nerve atrophy is being carried out with increasing frequency. Vincent [1a] went so far as to raise the question whether one should not operate in all cases of "tabetic optic nerve atrophy." He summed up the question by saying that it is not possible to give a final answer as to the propriety of such intervention and that the results of more operations must be awaited. Vincent [1a] made these comments in the discussion on a case of syphilitic optic nerve atrophy in which he had removed the thickened chiasmatic arachnoid but the operation was not followed by improvement of vision. In general, the results of this exploratory operation on syphilitic patients with optic nerve atrophy have been conflicting, some observers reporting little, if any, improvement of vision, while others are enthusiastic about the procedure. In Cushing's [12] patient with optic nerve atrophy due to congenital syphilis, the removal of the thick arachnoidal adhesions did not lead to improvement of vision. Dandy [17] performed exploratory operations in 3 cases. In none was there any evidence of adhesive arachnoiditis, and the operative results were neither beneficial nor deleterious. Hausman,[14] on the other hand, observed adhesions around the optic chiasm in all 3 cases in which he operated, and after removal of the adhesions vision improved. The most enthusiastic advocates of the surgical treatment of primary syphilitic optic nerve atrophy have been Vail,[1b] Hausman [1c-e] and Schaub.[1f] They stated that if the operation is performed before it is too late improvement in vision may result. Schaub [1f] observed 10 cases of syphilitic optic nerve atrophy treated surgically. In only 1 of these did the process progress to blindness. The condition in the others remained stationary or showed slight visual improvement. However, the criticism must be made that

17. Dandy, W. E., cited by Moore, J. E.; Hahn, R. D.; Woods, A. C., and Sloan, L.: The Treatment of Syphilitic Primary Optic Atrophy, Am. J. Syph., Gonor. & Ven. Dis. **26**:407, 1942.

in most cases of syphilitic optic nerve atrophy in which operation was performed not enough time had elapsed before the cases were reported to justify convincing conclusions.

Moore and Woods [17] stated the belief that in spite of the negative result in some instances, surgical exploration of the chiasmic area is justified in cases of syphilitic primary atrophy of the optic nerves in which visual failure is progressive in spite of malarial therapy, which at that time was the most efficacious mode of treatment. This was also my advice before the present histopathologic study disproved the theory that syphilitic optochiasmatic arachnoiditis is the underlying cause of optic nerve atrophy. The question arises as to the effect the conclusions of this study will have on the suggestions of such outstanding authorities on syphilitic optic nerve atrophy as Moore and Woods, although they admitted that, in their opinion, the results of operation were not hopeful, to say the least.[18] Or should one listen to the advice of Cushing,[12] who counseled all to strive for the avoidance of futile operations in cases of primary optic atrophy?

The final decision must be left to the physician who is in charge of the patient with syphilitic optic nerve atrophy. That a decision will be difficult is indicated by the favorable reports of surgical intervention by other surgeons. But it must be emphasized that most such cases concern patients with failing vision in the early stages of syphilis. Alpers and Yaskin [19] described a case of neurosyphilis with failing vision in which there was no response to medical treatment. A transfrontal craniotomy was performed, and the removal of chiasmatic arachnoiditis resulted in complete relief from headache and disturbance of vision. On the other hand, in a similar case of neurosyphilis in the early stages François [20] did not see any visual improvement after operation, but later, with the use of fever therapy and sulfur in oil, vision improved in one eye. The other eye remained blind. In these instances there was also choked disk, which is rare in cases of late neurosyphilis and is practically never present in cases of primary syphilitic optic nerve atrophy. The pathologic process underlying loss of vision, if a choked disk is present, is difficult to ascertain. In rare instances papilledema is due to the presence of a gumma, producing generalized intracranial pressure.[14] Or the papilledema may be due to syphilitic retrobulbar neuritis, confined to the most anterior portion of the orbital

18. Moore, J. E., and Woods, A. C.: The Pathology and Pathogenesis of Syphilitic Primary Optic Atrophy: A Critical Review, Am. J. Syph., Gonor. & Ven. Dis. **24**:59, 1940.

19. Alpers, B. J., and Yaskin, J. C.: Choked Disc in Syphilis of the Nervous System, Am. J. M. Sc. **190**:333, 1935.

20. François, J.: Arachnoïdite optochiasmatique syphilitique et pyrétothérapie, Bull. et mém. Soc. franç. d'opht. **50**:185, 1937.

portion of the optic nerves.[21] If vision improves after exploration of the chiasm, one is justified in attributing the favorable result to the operation. However, one should not forget that cases of spontaneous recovery of vision and subsidence of papilledema in the earlier stages of syphilis have been reported by Wilbrand and Saenger [21] in which the patient received only routine antisyphilitic treatment, or no therapy at all.

CONCLUSIONS

Recent theories have attributed the cause of primary syphilitic atrophy of the optic nerves to syphilitic optochiasmatic arachnoiditis, and surgical intervention has been recommended. On the basis of a histologic study of 12 cases of syphilitic primary atrophy of the optic nerves, the propriety of surgical intervention is discussed.

In 4 cases of syphilitic atrophy of the optic nerves no arachnoidal adhesions were present at all, and in 2 other cases the slight arachnoidal thickening could be considered as still within normal limits. In the other 50 per cent of cases there was definite syphilitic arachnoiditis in the optochiasmatic region. In these cases the pronounced thickening of the arachnoid, burying the optic nerves, the chiasm and, at times, the third and other cranial nerves, suggested from the gross appearance alone that the arachnoidal process could be implicated in the atrophy of the optic nerves. Microscopic examination corrected this erroneous impression, revealing that the thickened arachnoid passed harmlessly over the optic nerves and chiasm, leaving no signs of pressure, such as constrictive grooves in the optic nerves.

Primary syphilitic optic nerve atrophy is essentially the result of an inflammatory process in the intracranial portion of the optic nerves and in the chiasm. The inflammation has its origin in a basilar syphilitic meningitis, which in some instances produces an optochiasmatic arachnoiditis and in others leaves the basilar arachnoid grossly unaltered.

Surgical removal of the arachnoidal adhesions will be of little, if any, benefit because the inflammatory process within the optic nerves and chiasm remains unaltered by the operative procedure.

The most efficacious treatment of primary syphilitic optic nerve atrophy at the present time is malarial therapy,[5] aided by a course of concomitant and subsequent injections of penicillin, with 5,000,000 units in each course.

Central State Hospital.

21. Wilbrand, H., and Saenger, A.: Die Neurologie des Auges, Wiesbaden. J. F. Bergmann, 1913, vol. 5, p. 246.

OCULAR INJURY DUE TO SULFUR DIOXIDE

I. Report of Four Cases

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SULFUR dioxide in high concentration in the form of the liquefied gas commonly used in domestic refrigerators is an occasional cause of serious ocular injury. Accidental spraying of liquefied sulfur dioxide into the eyes of persons working on refrigeration machines has in some instances permanently reduced vision to light perception through production of corneal opacification and vascularization. The manner in which sulfur dioxide causes such severe damage is conjectural. In the present report, 4 cases of ocular injury due to sulfur dioxide are described, and in a subsequent report an experimental study will be presented aimed toward an elucidation of the means by which sulfur dioxide causes the damage.

Several previous descriptions of ocular injury due to liquid sulfur dioxide have been presented. A report of an accident involving squirting of liquid sulfur dioxide into the face was given by Kennon [1] (1927), who noted recovery of 20/15 vision following superficial corneal and conjunctival injury. He drew the conclusion that sulfur dioxide is relatively innocuous, but this impression was not confirmed in the experience of Clark,[2] who described 2 cases in which exposure to liquid sulfur dioxide resulted in serious corneal opacification and loss of vision.

Other instances of injury by sulfur dioxide refrigerant, with the outcome varying from complete recovery to dense corneal opacification, were noted, but not described in detail, by Shafer (cited by Clark [2]) and Goldburgh and Gouley.[3] A single instance of injury of the cornea and conjunctiva from liquid sulfur dioxide which was successfully treated with an amniotic membrane graft is included in a series of cases of caustic

From the Howe Laboratory of Ophthalmology, Harvard Medical School, and the Massachusetts Eye and Ear Infirmary.

1. Kennon, B. R.: Report of a Case of Injury to Skin and Eyes by Liquid Sulfur Dioxide, J. Indust. Hyg. **9**:486-487, 1927.

2. Clark, C. P.: Accidental Freezing of the Eye by Sulfur Dioxide, Am. J. Ophth. **19**:881-884, 1936.

3. Goldburgh, H., and Gouley, B.: Sulfur Dioxide Chemical Pneumonia; Report of a Case with Recovery Following Accidental Explosion of a Refrigerator, Unit. Ann. Int. Med. **18**:237, 1943.

burns studied by Sorsby and Symons.[4] Inquiry among a number of other ophthalmologists revealed that several had seen patients with ocular injuries from sulfur dioxide. Presumably, owing to the occurrence of a considerable number of unreported accidents, the presence of an ocular hazard appears to be generally recognized among persons using liquid sulfur dioxide in the refrigeration, as well as in the petroleum, industry.

When only the gaseous form of sulfur dioxide is employed, as in magnesium foundries, ocular reactions are, by contrast, relatively mild. This difference is no doubt due to the warning characteristics of the gas, which permit avoidance of excessive exposure. Whereas accidental contamination with the liquid occurs with such suddenness as to preclude effective reflex self protection, exposure to the gas produces symptoms which make its presence obvious, and even unbearable, at lower concentrations than those which cause ocular damage. The warning symptoms and the concentrations at which they occur have been determined by a number of observers (Ogáta,[5] Lehmann,[6] Ronzani[7] and Holmes and others[8]) and are considered to consist of a characteristic pungent smell, appreciable at a concentration of 3 to 5 parts per million of air by volume; irritation of the throat, at a concentration of 8 to 12 parts per million, and coughing, painful breathing and a sensation of burning of the eyes, at a concentration of 20 parts per million. On account of these unpleasant symptoms, it is considered that 10 parts of sulfur dioxide per million of air is the maximum concentration tolerable for long exposures and that 50 to 100 parts per million is the maximum for exposures of one-half to one hour. However, an appreciable increase in tolerance is noted among persons chronically exposed.

Conjunctival inflammation has often been mentioned as a frequent consequence of prolonged exposure to high concentrations (Flurry and Zernik,[9] Kehoe and associates[10] and Humperdinck[11]) and has at times

4. Sorsby, A., and Symons, H. M.: Amniotic Membrane Grafts in Caustic Burns of the Eye, Brit. J. Ophth. **30**:337-345, 1946.

5. Ogáta, M.: Ueber die Giftigkeit der schwefligen Säure, Arch. f. Hyg. **2**: 223, 1884.

6. Lehmann, K. B.: Experimentelle Studien über den Einfluss technisch und hygienisch wichtiger Gase und Dämpfe auf den Organismus, Arch. f. Hyg. **18**: 180-191, 1893.

7. Ronzani, E.: Ueber den Einfluss Einatmungen reizender Gase der Industrien auf den Verteidigungskräft des Organismus gegenüber den infektiven Krankheiten, Arch. f. Hyg. **67**:285, 1908.

8. Holmes, J. A.; Franklin, E. C., and Gold, R. A.: Report of the Selby Smelter Commission, Bulletin 98, United States Department of Interior, Bureau of Mines, 1915, pp. 172-175.

9. Flurry, F., and Zernik, F.: Schädliche Gase, Dämpfe, Nebel, Rauch- und Staubarten, Berlin, Julius Springer, 1931, p. 143.

been sufficient to necessitate change of occupation (Lewin and Guillery[12]). However, permanent ocular damage from occupational or accidental exposure to gaseous sulfur dioxide appears to be rare and is apparently unlikely to occur even in acute, nearly lethal exposures to the gas. Such conclusions may be drawn from the report of Rostoski and Crecelius[13] on the consequences of exposure of 33 men to sulfur dioxide for eight to forty-five minutes in high enough concentrations to cause the death of 10 and to leave 18 with chronic bronchitis, emphysema and bronchiectasis. Although all the men were said to have had severe inflammation of the eyes and oral mucous membrane immediately after the accident, a persistent ocular disturbance ("conjunctival catarrh") was noted in only 1 survivor. In other instances of accidental exposure to gaseous sulfur dioxide little attention has been paid to the ocular inflammation, whether acute or chronic (Humperdinck,[11] Wiese,[14] Goldburgh and Gouley[3]).

In contrast to the reports already mentioned is that of Strebel,[15] in which emphasis was placed on the presence of a superficial central punctate keratitis characteristically occurring in the manufacture of viscose and attributed by him to the action of sulfur dioxide. As pointed out by Knapp,[16] Strebel was apparently in error as to the cause of the disturbance. Sulfur dioxide is not ordinarily employed in the manufacture of viscose, and none of the commoner symptoms of exposure to sulfur dioxide were noted. Furthermore, it appears that the condition described by Strebel was identical with that subsequently considered by other investigators to be due to the hydrogen sulfide which is formed in the viscose process (Hortsch,[17] Barthelmy,[18] Rodenacker[19]).

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10. Kehoe, R. A.; Machle, W. F.; Kitzmiller, K., and LeBlanc, T. J.: On the Effects of Prolonged Exposure to Sulfur Dioxide, J. Indust. Hyg. **14**:159-173, 1932.

11. Humperdinck, K.: Zur Frage der chronischen Einwirkung von Schwefeldioxydgasen, Arch. f. Gewerbepath. u. Gewerbehyg. **10**:4-18, 1940.

12. Lewin, L., and Guillery, H.: Die Wirkungen von Arzneimitteln und Giften auf das Auge; Handbuch für die gesamte ärztliche Praxis, Berlin, A. Hirschwald, 1905, vol. 1 and 2.

13. Rostoski, O., and Crecelius: Zur Kenntnis der Sulfitgasvergiftungen, Deutsches Arch. f. klin. Med. **168**:107, 1930.

14. Wiese, E.: Untersuchungen in einer Leichtmetallgiesserei, abstracted, Zentralbl. f. Gewerbehyg. **28**:109, 1941.

15. Strebel, J.: Durch SO_2 verursachte Augenschädigungen (spez. zentrale punktförmige Viskoseverätzung der Hornhäute): Schutz durch Maskenbrille mit Zinkkohlefilter, Schweiz. med. Wchnschr. **53**:560-561, 1923.

16. Knapp, P.: Zur Frage der Keratitis traumatica infolge Einwirkung von Gasen, Schweiz. med. Wchnschr. **53**:702, 1923.

17. Hortsch, W.: Schwefelwasserstoff die Ursache der Augenerkrankungen in der Viskose-Kunstseidenindustrie, Veröffentl. a. d. Geb. d. Volksgesundhdienst. **47**: 669-734, 1937.

(Footnotes continued on next page)

REPORT OF CASES

CASE 1.—In August 1941, E. L., a man aged 27, with previously normal eyes and normal health, received a spray of sulfur dioxide and oil in both eyes from the explosion of a refrigerator on which he was working. There was immediate blurring of vision, but little discomfort. His eyes and face were washed with water, but the attention of an ophthalmologist was sought only after four days, when ocular pain and photophobia became considerable. Vision at that time permitted counting of fingers at 8 feet (240 cm.) with the right eye and at 5 feet (150 cm.) with the left eye. There was gray opacity of both corneas with some conjunctival edema and erosion, especially in the right eye. Despite treatment with a bland ointment and atropine, the photophobia, epiphora and intense conjunctival injection persisted, but vision in the left eye improved to 20/40 in the next four months. Vision in the right eye never improved beyond 20/200 and in four years was reduced to distinguishing light and dark. Loss of vision in the right eye was due to corneal opacity, which in the early stages had appeared diffuse and infiltrative, but after four years was characterized by a dense central plaque, surrounded with a halo of gray infiltration and extensive superficial and deep vascularization. A small central area stained with fluorescein at times. Because of incapacitating discomfort from severe photophobia and a sensation of burning, the cornea of the right eye was covered with a conjunctival flap, giving the patient nearly complete relief for the first time in four and one-half years.

CASE 2.—H. B., a man aged 52, in normal health except for his eyes, was seen for the first time ten years after the explosion of a sulfur dioxide refrigerator in his face. His face and eyes had been heavily contaminated with oil and sulfur dioxide, which he could make little attempt to wash off because the accident occurred at some distance from running water. He had immediate serious diminution in vision, which did not improve. Ten years after the accident he could perceive only hand movements at 5 feet with the right eye and at 3 feet (90 cm.) with the left eye but had good light projection. Leukomas of both corneas, with superficial vascularization, were present. There was pronounced symblepharon of both eyes, with thick bands of tissue extending from the fornices to the cornea. The appearance at this stage is shown in the figure. An optical iridectomy was done in the left eye several years after the accident. Later, a resection of a portion of the corneal scar in the right eye and transposition of the symblepharon tissue, followed by roentgen irradiation of the vascularized cornea, was of no apparent benefit.

CASE 3.—F. K., a man aged 21, and his brother, A. K. (case 4), received a spray of sulfur dioxide and oil in both eyes from a refrigerator on which they were working. Since discomfort was slight, although vision was blurred, efforts at decontamination consisted principally in wiping their faces and eyes. Two hours later there were edema of the lids, blepharospasm and conjunctival edema, with grayness of the corneas, which stained faintly with fluorescein in the area of the palpebral fissures. In addition to injuries of the eyes, both patients received superficial burns of the mucous membranes of the lips, tongue and nose, with temporary loss of sense of taste and smell, as well as some tracheal irritation.

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18. Barthelmy, H. L.: Ten Years Experience with Industrial Hygiene in Connection with Manufacture of Viscose Rayon, J. Indust. Hyg. **21**:141-151, 1939.

19. Rodenacker, G.: Die gewerblichen Gefahren des Schwefelwasserstoffes, Med. Klin. **37**:215-217, 1941.

In case 3 the immediate signs were all more prominent in the left eye than in the right. Three days after exposure vision was 20/30 in the right eye and 20/40 in the left eye. There was some superficial opacity of the left cornea, and both corneas stained in part. The conjunctivas were still intensely injected and edematous, with a number of small hemorrhages and pale areas of vascular thrombosis, particularly in the left eye.

By the end of the first week the relatively mild degree of involvement of the right eye was obvious, for by then the cornea was practically normal, and in two or three weeks after injury this eye had entirely regained its normal appearance. On the other hand, the more serious nature of the injury to the left eye was suggested during the first week by the appearance of irregularity of the endothelium, slight stromal edema and some opacification. Increased prominence of the corneal nerves was also noted in this eye and the cornea was definitely anesthetic.

For two to three weeks after injury small areas of the cornea of the left eye stained irregularly, and opacification gradually increased in both the superficial and the deep stroma of the temporal portion. This was soon accompanied with superficial and interstitial vascularization. During the first two months the central and temporal portions of the corneal stroma became heavily vascularized. However, during the third to the fifth month there was appreciable clearing.

Appearance of the eyes ten years after injury by sulfur dioxide (case 2).

At no time did the patient have any real pain, although in the first several weeks there were considerable photophobia and some scratching sensation. Mydriasis was maintained with atropine, and subsequently with scopolamine for four months. During this time there was no elevation of intraocular pressure or evidence of iritis.

CASE 4.—A. K., a man aged 28, received a spray of sulfur dioxide and oil in his eyes in the same accident as that sustained by his brother (case 3). He experienced the same relatively slight discomfort but had more pronounced immediate blurring of vision. Two hours later there were severe conjunctival edema, blepharospasm and grayness of the corneas, which stained faintly with fluorescein. The lids were edematous but did not appear to be injured. Three days later both corneas were gray with a grossly irregular, lusterless surface, more noticeable in the right eye. Both corneas stained moderately with fluorescein and were completely anesthetic. The conjunctivas were edematous and pale, with thrombosis

of all visible vessels. Vision was reduced to the perception of hand movements in the right eye and to counting fingers at 3 feet in the left eye.

By the end of the first week the dense grayness and irregularity of the anterior surface of the corneas were lost centrally, and vision was considerably improved. However, the stroma of both corneas was still moderately thickened, and the endothelium was gray and irregular. The corneal nerves were abnormally prominent. The conjunctival vessels were still thrombosed; but many small hemorrhages had now appeared, so that the original pallor of the conjunctivas was replaced with a beefy appearance.

During the remainder of the first month the corneas remained fairly clear, although there was persistent staining, more conspicuous in the right eye, and faint laminate opacities could be seen in the stroma, both at the anterior surface and in the central portion. Swelling of the stroma did not progress, and the grayness and irregularity of the endothelium were gradually replaced with a granular appearance. In this period the patient complained of severe photophobia and frontal headaches.

During the second month there were increasing infiltration and opacification of both corneas, with occasional remissions and progressive, dense interstitial vascularization. The anterior surfaces continued to be grossly uneven and to stain irregularly with fluorescein. The photophobia and headache subsided.

In the third month after injury the conjunctivas, which were still severely injected, began to overgrow the corneas, but there appeared to be no tendency to formation of symblepharon.

By the fourth month vision was reduced to perception of hand movements as shadows, owing to corneal opacification and extensive superficial and interstitial vascularization.

During the period described the patient was treated with atropine and then with scopolamine, as was his brother (case 3). At no time was the ocular tension found to be elevated, and no deposits were observed on the posterior surface of the cornea.

COMMENT

From the cases described here, it appears that sulfur dioxide causes almost immediate optical alterations in the cornea, most obviously due to changes in the corneal epithelium, which, though opacified, remains adherent to the stroma, as in acid burns. At first there is only minor discomfort, even with serious injury, probably because of damage to the corneal nerves and resultant anesthesia. The patient may become aware of the seriousness of his injury only during the next several hours or days, when there may be further decrease in vision. There are then considerable swelling of the lids and thrombosis of the conjunctival vessels. Loss of the opaque corneal epithelium in several days permits somewhat better vision and in cases of severe injury reveals more clearly the evidences of deeper injury, in the form of stromal edema, opacity of the corneal nerves and a grayness and irregularity of the endothelium. Such deeper changes resemble those produced by the penetrating action of alkalis, and, similarly, the subsequent course may be characterized by the occurrence of stromal infiltrates and interstitial vascularization. In the eyes observed, serious stromal changes of this nature occurred

with only moderate thickening of the stroma, suggesting that minor impairment of semipermeability of the endothelium may be involved. In these cases there was no problem of either iritis or glaucoma. Except for corneal scarring, conjunctival overgrowth of the cornea or formation of symblepharon appears to be the most frequent complication.

In their principal features, the cases reported here are similar to those of other authors. Thus, the slight degree of injury observed by Kennon [1] in his single case has counterparts in the left eye in case 1 and in the right eye in 3, while the effects described by Clark [2] resemble those observed in some of the other eyes in the present cases. The interpretations of these authors, however, find no support in the present observations. The belief that sulfur dioxide is relatively innocuous is certainly unfounded, while the claim that sulfur dioxide produces its ocular injuries through freezing could not be substantiated without considerable additional information, which is unavailable clinically.

To supply some of the information necessary for evaluation of the mode of action of sulfur dioxide in producing ocular injuries, an experimental investigation has been undertaken and will be reported separately.

SUMMARY

Ocular injuries resulting from spraying of liquid sulfur dioxide and oil into both eyes in 4 cases were characterized in most instances by immediate damage to the corneal epithelium, as in acid burns, with underlying stromal and endothelial injury, as in alkali burns. In the cases of mildest injury the outcome was complete recovery, while in the cases of severest damage dense opacification followed corneal infiltration and interstitial vascularization.

243 Charles Street (14).

OCULAR INJURY DUE TO SULFUR DIOXIDE

II. Experimental Study and Comparison with Ocular Effects of Freezing

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THE ACCIDENTAL injuries of the eye produced by liquefied sulfur dioxide which have been reported by myself [1] and others have usually been severer than those produced by other substances with similar moderately acidic properties. To account for the greater toxicity of sulfur dioxide, previous observers have proposed some rather unusual mechanisms based on the physical and chemical peculiarities of the noxious agent. Experiments carried out in this laboratory indicate that a relatively simple mechanism, different from those previously proposed, is responsible in large measure for the peculiar toxicity of sulfur dioxide.

The following two hypotheses have previously been advanced to explain the severity of ocular injury produced by liquid sulfur dioxide. It has been assumed by some investigators that injury of the eye is due to freezing produced by the rapid evaporation of the liquefied gas (Kennon,[2] Clark [3]), while others have assumed that injury is caused by the oxidative formation of sulfuric acid from sulfur dioxide on the moist mucous membrane surfaces (Flurry and Zernik,[4] Rost [5]). That sulfurous acid, which is formed directly on contact of sulfur dioxide with water, could itself be sufficiently injurious to produce the damage observed has not been seriously considered, perhaps because sulfurous acid is a relatively weak acid, similar to phosphoric acid, and might therefore not be expected to cause the serious disturbances observed clinically.

From the Howe Laboratory of Ophthalmology, Harvard Medical School, and the Massachusetts Eye and Ear Infirmary.

1. Grant, W. M.: Ocular Injury Due to Sulfur Dioxide: I. Report of Four Cases, Arch. Ophth, this issue, p. 755.

2. Kennon, B. R.: Report of a Case of Injury to Skin and Eyes by Liquid Sulfur Dioxide, J. Indust. Hyg. **9**:486-487, 1927.

3. Clark, C. P.: Accidental Freezing of the Eye by Sulfur Dioxide, Am. J. Ophth. **19**:881-884, 1936.

4. Flurry, F., and Zernik, F.: Schädliche Gase, Dampfe, Nebel, Rauch und Staubarten, Berlin, Julius Springer, 1931, p. 143.

5. Rost, E., in von Bock, J., and others: Handbuch der experimentellen Pharmakologie, Berlin, Julius Springer, 1927, vol. 3, pt. 1, pp. 389-417.

The evidence cited to support the idea that frostbite is an important factor is the indefinite report by Carroll [6] of a case in which partial epithelial denudation of the cornea and temporary conjunctival congestion developed after exposure to a cold wind on two successive days. Similarly, keratitis epithelialis, resolving completely in three days, was reported by Colombo [7] as occurring in an aviator exposed to wind and low temperature for several hours. However, there seems to be little similarity to injury with sulfur dioxide in either case. Furthermore, there appears to be no experimental information on the effects of freezing of the eye which could be used as a basis for comparison.

The evidence that the injury results from oxidation of sulfur dioxide to sulfuric acid is also unsatisfactory. It is based on the fact that the major portion of sulfurous acid or its salts (bisulfite or neutral sulfites) which are ingested or injected can be accounted for in the form of sulfate in the urine (Rost and Franz [8]) and that little sulfite can be found in the circulating blood after the ingestion of large amounts of the sulfite. These observations led to the assumption that the oxidation to sulfate occurred in the lining of the gastrointestinal tract, but it is noteworthy that sulfite introduced directly into the blood stream also disappears rapidly.[8] From such evidence it has been inferred that oxidation of sulfur dioxide similarly occurs on the mucous surfaces of the respiratory system and elsewhere, with production of enough sulfuric acid to account for the lesions produced by exposure to sulfur dioxide. However, the formation of sulfuric acid in significant amounts on mucous membrane surfaces has not been demonstrated directly.

Previous experiments on ocular lesions due to sulfur dioxide have been confined to cursory observations and limited to the effect of exposure of animals to mixtures of the gas and air. Ogáta [9] reported clouding of the corneas of rabbits, guinea pigs and mice after exposure for four hours to a concentration of 400 parts per million of air by volume and clouding in 1 guinea pig after exposure for one hour to a concentration of 1,000 parts per million. Weedon and associates [10] mentioned the occurrence of corneal opacification in mice and guinea

6. Carroll, F.: Frost Bite of the Cornea, Am. J. Ophth. **16**:994, 1933.

7. Colombo, G. L.: Bilateral Changes in the Corneae Following Exposure to Cold in an Airman, Brit. J. Ophth. **5**:553-558, 1921.

8. Rost, F., and Franz, F.: Vergleichende Untersuchung der pharmakologischen Wirkungen der organische gebundenen schweflichen Säuren und des neutralen Schwefligsäuren Natriums: II., Arb. a. d. k. Gsndhtsamte. **43**:187-303, 1912.

9. Ogáta, M.: Ueber die Giftigkeit der schwefligen Säure, Arch. f. Hyg. **2**:223-245, 1884.

10. Weedon, F.; Hartzell, A., and Setterstrom, C.: Effects on Animals of Prolonged Exposures to Sulfur Dioxide, Contrib. Boyce Thompson Inst. **10**:281-324, 1939.

pigs exposed to concentrations of 110 to 300 parts per million of air for approximately three days, and McNally [11] noted severe conjunctivitis and corneal opacity in guinea pigs killed by exposure to 10,000 parts of sulfur dioxide per million of air for fifteen minutes. No experimental investigation of the effect of exposure to liquid sulfur dioxide has been made.

Because of this lack of information on the possible physical and chemical effects of liquid sulfur dioxide on the eye, and the consequent uncertainty regarding the mechanism of production of the lesions observed clinically, the following experimental investigation and comparison of these effects was undertaken.

EXPERIMENTAL INVESTIGATION

Effect of Freezing.—Owing to the paucity of information on the consequence of brief freezing of the living eye, observations were made on the effect of exposing the rabbit eye to a refrigerant liquid. In order to permit clear differentiation of physical and chemical effects in these experiments, use was made of a chemically inert, relatively nontoxic refrigerant, "freon-12" (dichlorodifluoromethane). This refrigerant has physical properties similar to those of sulfur dioxide but a relatively innocuous chemical nature, as confirmed by the observation that exposure of a rabbit's eye to a rapid stream of the pure gas at room temperature for ninety seconds caused no irritation or injury of the eye apparent grossly, on application of fluorescein or on biomicroscopic examination during the ensuing three days. Liquefied "freon," on the other hand, may be assumed to produce a temperature as low as, or lower than, that produced by sulfur dioxide when permitted to evaporate in contact with the eye, since at atmospheric pressure its boiling point is —28 C., as compared with that of —10 C. for sulfur dioxide.

Experiments with freezing were first carried out with a mixture of liquefied "freon" and oil, analogous to the mixtures of sulfur dioxide and oil to which the patients were exposed in the accidents previously reported.[1] Each of 2 rabbit eyes was held open by means of a speculum and was subjected at a distance of about 6 inches (15 cm.) to the full blast of a spray obtained by opening wide the valve on an inverted tank of the "freon"-oil mixture. The duration of exposure to the spray was approximately one second, which is presumably somewhat longer than a human being would keep his eye open in similar circumstances. The corneas and margins of the lids became white and hard during the spraying, but regained their normal appearance during the next five or ten seconds. Biomicroscopic examination revealed no

11. McNally, W.: The Use of Sulfur Dioxide as a Refrigerant, Indust. Med. **8**:234-238, 1939.

abnormality immediately. During the next few hours there appeared slight vascular congestion and edema of the nictitating membrane and conjunctiva. Moderate edema of the corneal epithelium gradually developed, progressing to denudation of a small central area in twenty-four hours. Within seventy-two hours of the exposure and thereafter the eyes appeared normal, both grossly and microscopically.

Freezing of the eye for a few seconds, such as might conceivably occur in an accidental exposure, thus produced disturbances which were mild and transient. For more prolonged freezing, liquid "freon" was sprayed onto 1 rabbit eye for five seconds and onto another eye for thirty seconds. The corneas of both eyes became immediately opaque, dense white and hard. The nictitating membrane and the lids were solid. In one to two minutes the tissues thawed and the normal transparency of the cornea and appearance of the eyes were completely regained. However, in about five minutes the corneal endothelium of the eye which had been exposed for thirty seconds was seen on biomicroscopic inspection to have become gray with dark round and oval defects. There rapidly followed in this eye shedding of most of the endothelium in sheets, which could be seen settling slowly through the aqueous humor. In the eye exposed for five seconds, gray opacity and numerous defects of the endothelium were apparent in fifteen minutes, but shedding was less extensive. At this time, chemosis of the conjunctiva and injection of the iris were apparent in both eyes, but the corneas did not stain. At thirty to forty-five minutes thickening of the corneas and faint diffuse staining with fluorescein were observed. During the next several hours the corneas became swollen to several times their normal thickness and acquired a translucent, bluish appearance. They continued to take a diffuse stain with fluorescein. The conjunctiva, nictitating membrane and margin of the lids of the eye exposed for thirty seconds underwent a severe reaction, with partial necrosis and considerable purulent discharge. Within ten days the cornea of this eye became opaque, yellow and sloughed. The reactions were considerably milder in the eye exposed for five seconds. This eye showed improvement in ten days and appeared practically normal in six weeks. The cornea was clear except for a small gray patch in the center, where some edema of the stroma and epithelium persisted. There was little increased vascularity of the cornea at the limbus.

Effect of Sulfur Dioxide Without Freezing.—The effects of sulfur dioxide were next examined under conditions in which there could be no question of freezing. Exposures of rabbits and guinea pigs to mixtures of sulfur dioxide and air at room temperature in a constant flow exposure chamber confirmed the production of keratitis and corneal clouding under conditions of time and concentration similar to those reported by other investigators. The results are given in table 1.

Only by lethal concentrations could severe ocular lesions be produced when the whole animal was exposed. In order to observe the production and subsequent course of severe ocular lesions, it was necessary to expose the eyes only.

Such experiments were performed on rabbits by placing the animal in a well ventilated fume hood while the eye was exposed to a rapid current of gas from a tube held within 1 inch (2.5 cm.) of the cornea. The lids were separated, and the nose of the animal was shielded manually during exposure. An exposure of five seconds to a stream of pure gaseous sulfur dioxide at room temperature was observed to produce corneal injury comparable to that encountered in patients exposed to the liquid sulfur dioxide, and this period of exposure was used as a standard for subsequent investigations of the mechanism of injury. The longer time of exposure required by the gas to produce an injury comparable to that from the liquid may be explained by the fact that while 1 cc. of the liquid contains 1.4 Gm. of sulfur dioxide, 1 cc. of the gas contains only 0.0026 Gm.

This exposure for five seconds caused intense superficial grayness of the cornea, beginning immediately and increasing for one to two

TABLE 1.—*Effects of Exposure of Animals to Mixtures of Sulfur Dioxide and Air*

Sulfur Dioxide, P. P. M.*	Exposure Time	Animals Used	Results
145 (120-170)	10 days	2 rabbits	No keratitis; animals appeared moribund
460-490	30 hr.	2 rabbits; 3 guinea pigs	All had keratitis; all dead within 72 hr. after end of exposure
800-1,000	24 hr.	2 rabbits; 3 guinea pigs	All had keratitis and corneal opacity; all dead within 24 hr. after end of exposure

* P. P. M. indicates parts of sulfur dioxide per million of air by volume.

minutes. Chemosis and injection of the conjunctiva appeared within a few minutes and were soon accompanied with a milky discharge. For several days the cornea was persistently gray, with the opacity occurring predominantly in its superficial layers but extending also in a granular and laminar fashion throughout the thickened stroma. The epithelium was irregularly thickened and was lost from some areas. These epithelial abnormalities did not appear to be due simply to edema and were not appreciably altered by application of glycerin. In ten days the corneal opacity began to decrease somewhat, while interstitial vascularization extended 2 to 3 mm. from the limbus. The process of slight clearing and increasing vascularization progressed slowly until in six months there were extensive vascularity with the vessels meeting in the center, and moderate opacity.

Histologic sections of rabbit eyes which had received the standard exposure of five seconds to pure gaseous sulfur dioxide were examined at intervals of fifteen minutes to six months after exposure. The pathologic changes observed corresponded in general to those described

by Friedenwald, Hughes and Herrmann [12] as characteristic of severe acid burns. The only possibly distinguishing feature of sulfur dioxide burns was a striking predominance of eosinophils in the corneal infiltrate at all stages. Moreover, there was relatively little iritis in these eyes. As described for the acid burns, the corneal endothelium was not obviously damaged.

Effect of Hydration Products of Sulfur Dioxide.—Information on the chemical mechanism by which sulfur dioxide may cause the changes observed in the preceding experiment was sought by investigation of some of the chemical transformations which might be involved. It would be expected that sulfur dioxide in moist buffered tissue would primarily be converted into sulfurous acid, acidic bisulfites and neutral sulfites in proportions determined by the effectiveness of buffering, and that there might be differences in the toxicity of these various forms. Furthermore, the possibility of oxidation to a stronger acid was to be considered.

Since it was not feasible to determine the amount of each of these derivatives formed in the cornea on exposure to sulfur dioxide, the total sulfur dioxide in all forms was measured. It was then possible to introduce similar quantities of bisulfite and neutral sulfite alone into other corneas and to compare their toxicities. The rate of disappearance of sulfur dioxide and its derivatives was also measured, and tests were made for the formation of sulfuric acid.

The total quantity of sulfur dioxide present in all forms was measured in rabbit corneas excised immediately after exposure for five seconds to sulfur dioxide gas. Extracts of individual corneas in alcoholic potassium hydroxide solution were made and analyzed by a colorimetric method (Grant [13]). The concentrations of sulfur dioxide found immediately and at intervals after exposure are shown in the chart. The concentrations found in the conjunctiva and the aqueous are given in table 2 for comparison.

It may be observed from these data that the concentration of sulfur dioxide in all forms in the living cornea decreases exponentially with time, with a half-life of approximately fifteen minutes. Furthermore, the rise in concentration of sulfur dioxide in the aqueous humor immediately after exposure suggests that the cornea and conjunctiva are readily permeable to sulfur dioxide.

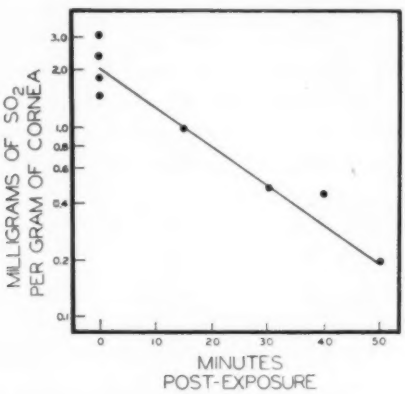
Qualitative testing of the neutralized corneal extracts by means of barium chloride failed to reveal an increase of sulfate such as might be found if a significant proportion of the sulfur dioxide were oxidized to sulfuric acid.

12. Friedenwald, J. S.; Hughes, W. F., and Herrmann, H.: Acid Burns of the Eye, Arch. Ophth. **35**:98-108 (Feb.) 1946.

13. Grant, W. M.: Colorimetric Determination of Sulfur Dioxide, Indust. & Engin. Chem. (Anal. ed.) **19**:345-346, 1947.

Comparative experiments to assess the relative rates of diffusion of sulfur dioxide from cornea into the air or into aqueous bathing fluids were performed by exposing buttons cut from beef corneas to sulfur dioxide gas for five seconds and then measuring the amounts residual after various periods of standing in air, water or a 5 per cent solution of sodium bicarbonate at room temperature. The half-life of the sulfur dioxide in air-bathed corneal buttons was approximately 240 minutes, while in those bathed by water or sodium bicarbonate it was 5 to 10 minutes. Thus, it appears that during the rapid disappearance of sulfur dioxide from the cornea in vivo diffusion into the air must be an insignificant factor.

To determine the toxicity of sulfur dioxide in the form of sulfite, a neutral 1.4 molar solution of sodium sulfite was dropped onto 2 rabbit eyes continuously for thirty minutes. Analysis of 1 cornea showed



Time relation of decrease in concentration of sulfur dioxide in all forms in the corneas of rabbits following acute exposure to the gas.

that a concentration was achieved equivalent to 2.15 mg. of sulfur dioxide per gram of cornea, equaling the average concentration found immediately after the exposures to the gas. Although this treatment caused intense conjunctival injection and chemosis, loss of epithelium from the center of the cornea and the presence of aqueous flare, no opacity was produced and the eye was apparently normal in two days.

The toxicity of bisulfite was investigated by irrigation of rabbit eyes for thirty minutes with 5.5 molar sodium bisulfite at its natural p_H of 3.8, producing a concentration in the cornea equivalent to 4.63 mg. of sulfur dioxide per gram of cornea. This concentration was somewhat greater than the highest concentration achieved with exposures to the gas. The damage caused by this treatment resembled that resulting from sulfur dioxide itself but was considerably milder than that produced by an exposure for five seconds. There were severe con-

junctival injection and chemosis, with grayness and irregularity of the corneal epithelium and swelling of the stroma. However, the ground glass appearance of the epithelium, which was not altered by glycerin and the translucent opacity of the stroma cleared completely without vascularization in ten days.

By comparison, it appears that sulfur dioxide must exert its injurious effect principally in the form of sulfurous acid, since neither the neutral sulfite nor the bisulfite produced injury of the severity observed in exposures to sulfur dioxide and the formation of sulfuric acid was negligible. The mechanism by which sulfurous acid might produce these injuries was, therefore, next to be investigated.

Effect of Sulfur Dioxide (or Sulfurous Acid) on Corneal Catalase.—An indication of whether exposures of the cornea to sulfur dioxide may be attended by inactivation of corneal enzymes was sought through

TABLE 2.—*Concentration of Sulfur Dioxide in Ocular Tissues*

Time Following Exposure	Cornea, Micrograms per Gm.	Conjunctiva, Micrograms per Gm.	Aqueous, Micrograms per Gm.
Immediate (30-90 sec.)	1,860	2,250	340
	1,470	2,920	484
	3,170	627	157
	2,410	1,780	39
Average	2,227	1,894	255
15 minutes	978	260	533
30 minutes	465	376	226
40 minutes	455	...	430
50 minutes	195	...	81
90 minutes	108	50	25

measurement of the activity of a single enzyme, catalase. The behavior of this enzyme was investigated only to obtain information on the nature of the changes in the cornea, and not to attempt identification of what specific enzymes might be involved in production of injury.

The catalase activity of single minced rabbit corneas was estimated by volumetric determination of the rate of liberation of oxygen from dilute hydrogen peroxide, using a micromodification of the method of Thompson.[14] One eye of each rabbit was exposed to pure sulfur dioxide gas for five seconds in the manner already described, and the other eye was used as an unexposed control. The corneas were excised, and catalase assay was performed immediately after exposure. The rate of liberation of oxygen ranged from 393 to 840 (average 650) cu. mm. per minute per gram of cornea for 5 normal corneas, whereas with 2 exposed corneas there was no measurable liberation of oxygen in fifteen minutes. These results are considered to show that an exposure

14. Thompson, R.: Simplified Apparatus for Catalase Determination, Indust. & Engin. Chem. (Anal. ed.) **14**:585, 1942.

to sulfur dioxide which will result in serious injury is immediately attended with changes within the cornea sufficiently drastic to cause inhibition of enzymes. However, it cannot be concluded that the injury to the cornea is due to inactivation of catalase alone, for in separate experiments in which corneal catalase was inhibited by means of hydroxylamine no opacification of the cornea resulted.

Comparative experiments to determine the effect of freezing on corneal catalase were carried out on excised cattle eyes. No significant difference was found between the activity of control corneas and that of corneas of eyes frozen with "freon" for either five or thirty seconds.

Effect of Sulfur Dioxide on Swelling Properties of the Cornea.—For the purpose of determining whether sulfur dioxide may produce, in addition to inhibition of enzymes, a gross alteration in the physical characteristics of the corneal stroma which is not revealed with the usual histologic technic, measurements were made of the turgescence properties of normal and of exposed corneas, employing the technic of Kinsey and Cogan.[15] Excised cattle eyes were used in these experiments, and the swelling of exposed corneal buttons was allowed to take place in running water so that residual acid would be removed. Five pieces of cornea were used for each determination, and the weights were compared after two thousand six hundred minutes was allowed for swelling. Normal corneal buttons increased in weight 550 per cent, while corneal buttons exposed for ten to fifteen seconds to sulfur dioxide gas increased only 134 per cent. In another set of measurements, the control corneal buttons increased 470 per cent in weight, while buttons from corneas exposed for five seconds to the gas increased 159 per cent. Thus, a length of exposure such as causes a severe corneal injury produces a significant alteration in the turgescence properties of the stroma.

This inhibition of turgescence was found to be persistent even though, on washing in water, the analytic value for sulfur dioxide was reduced to a quantity not significantly different from the blank value for cornea, which corresponded to approximately 0.5 per cent of the immediate post-exposure concentration. Since it has previously been ascertained that essentially complete recoveries of sulfur dioxide are obtained with the method of analysis employed, it appears that the amount of residual or fixed sulfur dioxide which could be associated with the inhibition of turgescence was not greater than approximately 30 micrograms per gram of cornea.

To determine whether sulfur dioxide solution differs notably from other acids in its ability to inhibit corneal swelling, the effect on swelling of exposures to several other acids was compared. Sets of 5 corneal buttons each were exposed by dipping for two minutes in 0.1 molar

15. Kinsey, V. E., and Cogan, D. G.: The Cornea: III. Hydration Properties of Excised Corneal Pieces, Arch. Ophth. **28**:272-284 (Aug.) 1942.

solutions of seventeen different acids, including sulfurous acid, all adjusted to a p_H of 2.0 with either hydrochloric acid or sodium hydroxide. The extent of swelling in running water for two thousand six hundred minutes was then measured. The results are given in table 3. The differences observed are no doubt dependent to some extent on differences in rate of penetration, and this factor will be further considered later. However, it is apparent from these measurements that sulfur dioxide solution has no outstanding effectiveness over solutions of other acids in impairing corneal turgescence when the acids have direct contact with the corneal stroma.

Determination of Permeability of the Cornea to Sulfur Dioxide.—A comparison was made of the permeability of the cornea to sulfur dioxide and to other acidic substances in order to determine whether the toxicity of sulfur dioxide to the eye may be enhanced by any superior properties of penetration. Such a possibility is suggested by the rapid

TABLE 3.—*Effect of Exposure to Various Acids on Subsequent Swelling of Cornea in Running Water*

Acid	Corneal Swelling *	Acid	Corneal Swelling
Control	420	Formic	189
Phenol	386	Phosphoric	158
Trichloroacetic	373	Lactic	150
Boric	308	Oxalic	150
Hydrochloric	295	Monochloracetic	144
Nitric	287	Acetic	143
Sulfuric	225	Maleic	133
Sulfurous	225	Sulfosalicylic	120
Nicotinic	196	Propionic	119

* The corneal swelling is expressed as the final weight in terms of the percentage of the original weight.

penetration of sulfur dioxide into the aqueous humor of exposed rabbit eyes apparent from the measurements of concentration given in table 2. Excised cattle corneas were fastened to the ends of glass tubes in the manner described by Cogan and Kinsey [16] to form a membrane separating fluid in a tube from fluid bathing the outside. Comparisons of the rate of penetration of acids into the cornea were made by covering the epithelial surfaces with 2 cc. of sulfurous acid or other acid while periodically determining the p_H of 2 cc. of water bathing the other side of the cornea. The times required for various acids to lower the hydrogen ion concentration on the other side of the cornea to p_H 5 were determined, and after each experiment the integrity of the epithelial barrier of each cornea was checked by estimation of its permeability to fluorescein. In order to facilitate comparison of the acids, they were all used in 0.1 molar concentration and were adjusted with either hydrochloric acid

16. Cogan, D. G., and Kinsey, V. E.: The Cornea: I. Transfer of Water and Sodium Chloride by Osmosis and Diffusion Through the Excised Cornea, Arch. Ophth. **27**:466-476 (March) 1942.

or sodium hydroxide to p_H 1.0 in one set of measurements and to p_H 2.0 in another. The results of these two sets of timing measurements are given in table 4, together with the dissociation constants of the acids employed.

It may be concluded from examination of these data that the cornea has a relatively high permeability to sulfurous acid which cannot be related simply to its dissociation characteristics. This high permeability can be explained, however, by the fact that sulfur dioxide, which in aqueous solution is in equilibrium with sulfurous acid, has considerable lipid solubility to facilitate its transfer through cellular membranes. Measurement of the distribution of sulfur dioxide between water and a typical lipid, tributyrin, showed that sulfur dioxide is, in fact, preferentially soluble in the lipid. Further evidence indicating that penetration of sulfurous acid is effected through a lipid-soluble phase was obtained in examination of the penetration of "latex" membranes, which unreported experiments by Dr. D. G. Cogan have shown to resemble the cornea in being most readily permeable to substances having a definite lipid-soluble phase. Sulfurous acid was found to pass through a "latex" membrane many times faster than phosphorus acid at a comparable concentration and hydrogen ion concentration.

TABLE 4.—*Comparison of Rates of Penetration of the Cornea by Various Acids in Vitro*

Acid	Time of Penetration (Min.) p_H 1.0	Time of Penetration (Min.) p_H 2.0	Dissociation Constant
Sulfurous	53	123	1.7×10^{-2}
Trichloroacetic	102	>400	2.0×10^{-1}
Monochloroacetic	129	165	1.4×10^{-3}
Formic	155	115	1.76×10^{-4}
Phosphoric	157	300	1.1×10^{-2}
Hydrochloric	157	>400	
Propionic	162	180	1.4×10^{-5}
Acetic	180	>400	1.75×10^{-5}
Maleic	280	>400	1.5×10^{-2}
Sulfuric	300	>400	
Sulfosalicylic	...	>400	
Nitric	...	>400	
Lactic	...	>400	1.38×10^{-4}

COMMENT AND CONCLUSIONS

Observations made in this study on the effect of freezing and of high concentrations of sulfur dioxide at room temperature leave little doubt that it is the chemical properties of liquid sulfur dioxide which are primarily responsible for corneal injury.

The injurious action of solutions of sulfur dioxide on tissue other than the eye has been known since Pfeiffer[17] (1890) described the

17. Pfeiffer, L.: Zur Kenntniss der giftigen Wirkung der Schwefligen Säure und ihrer Salze, Arch. f. exper. Path. u. Pharmakol. **27**:261-296, 1890.

production of protein coagulation, interference with blood supply and necrosis by the substance. The irritant effect and bactericidal action of sulfur dioxide have been noted in numerous subsequent reports. That sulfur dioxide exerts its toxicity principally in the form of sulfurous acid, as concluded in the present experiments on the eye, was previously indicated by Jacobj and Walbaum [18] in a consideration of gastric irritation and was clearly demonstrated by Rahn and Conn [19] in a study on yeast. The conclusion that sulfur dioxide produces an "acid burn" in the eye is supported by the similarity of the histologic changes to those of other acid burns.

When an explanation is sought for the greater toxicity of sulfurous acid than of similar acidic substances, it is observed that sulfurous acid does not have outstanding protein-denaturing properties as compared with other acids, and that, although it does inhibit enzymes, it may do so merely by lowering the p_H, as claimed by Pfeiffer.[17] In fact, the toxicity of sulfurous acid is particularly notable only where cellular structures are concerned, as in the cornea. According to the foregoing experiments, the peculiar susceptibility of cells to sulfurous acid may be explained by the ready penetration of sulfur dioxide through cell membranes, due to its considerable lipid solubility. Thus it appears that the severity of injury with liquid sulfur dioxide is in large part due to the easy penetration of a high concentration of sulfur dioxide through the semipermeable cellular barriers of the cornea, giving access to vital structural and enzyme proteins, which it denatures.

What specific reactions of sulfur dioxide are involved in its devitalizing action are undetermined, but it does seem possible to conclude, by comparison of the relative rates and p_H optima, that its reactions with disulfide linkages (Elsworth and Phillips [20]), thiamine (Williams and associates,[21] 1935) or with aldehydes are probably not the basis of its injurious effect.

SUMMARY

Freezing of the anterior portion of the living rabbit eye for several seconds produces mild and transient disturbance, while freezing for thirty to ninety seconds causes loss of the endothelium with consequent

18. Jacobj, C., and Walbaum, H.: Zur Bestimmung der Grenze der Gesundheitsschädlichkeit der schwefligen Säure in Nahrungsmitteln, Arch. f. exper. Path. u. Pharmakol. **54**:421-438, 1906.

19. Rahn, O., and Conn, J. E.: Effect of Increase in Acidity on Antiseptic Efficiency, Indust. & Engin. Chem. **36**:185-187, 1944.

20. Elsworth, F. F., and Phillips, H.: The Action of Sulfites on the Cystine Disulfide Linkages in Wool: II. The Influence of Temperature, Time and Concentration on the Reaction, Biochem. J. **35**:135-143, 1941.

21. Williams, R. R.; Waterman, R. E.; Keresztesy, J. C., and Buchman, E. R.: Studies of Crystalline Vitamin B: III. Cleavage of Vitamin with Sulfite, J. Am. Chem. Soc. **57**:536-537, 1935.

edema of the stroma and epithelium, changes unlike those produced in accidental ocular injury with liquid sulfur dioxide.

Lesions similar to those caused by liquid sulfur dioxide can be produced by several seconds' exposure to the pure gas at room temperature, a condition in which there is no question of freezing.

The concentration of sulfur dioxide in all forms in the rabbit cornea was measured at intervals after exposure and was found to decrease exponentially, with a half-life of approximately 15 minutes.

Introduction of neutral sulfite or bisulfite into the rabbit cornea in concentrations comparable to the total sulfur dioxide concentration of gas-exposed corneas does not produce comparably severe injury, and it is concluded that sulfur dioxide exerts its toxic effect principally in the form of sulfurous acid. No significant production of sulfuric acid was detected.

Sulfur dioxide impairs the turgescence properties of the corneal stroma, as well as inactivates corneal catalase.

The epithelium and stroma of the cornea have a relatively high permeability to sulfur dioxide, a property which is related to the lipid solubility of sulfur dioxide.

It is concluded that the production of severe ocular injury by liquid sulfur dioxide is not due to freezing or to the formation of sulfuric acid, as has formerly been postulated, but is the result of its ready penetration of the corneal epithelium in high concentrations and its action, principally as sulfurous acid, in denaturing corneal proteins, including enzymes.

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CHRONIC TEARING CURED BY REESTABLISHMENT OF NORMAL TEAR CONDUCTION PASSAGES

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CHRONIC tearing of the eye is usually due to abnormality of the tear conduction passages. These passages consist of (1) the eyelids; (2) the puncta and canaliculi, and (3) the tear sac, its prolongation downward into the nasolacrimal duct and that portion of the nose into which the nasolacrimal duct drains.

Chronic irritation arising from refractive errors and muscular imbalance occasionally causes chronic tearing. Psychic, glandular or reflex factors are infrequently involved. In cases of the latter type, a drop of an innocuous colored solution, e. g., 1 per cent fluorescein sodium, placed in each eye will be quickly transmitted into the nose. The comparative speed with which each eye so clears itself measures the efficiency of the tear-conducting apparatus of each eye. The presence, as well as the concentration, of the colored solution can be gaged by blowing each side of the nose separately into a paper tissue. A more efficient method is to seek for the colored solution with the aid of a cotton-tipped probe placed under the inferior turbinate bone, where the nasolacrimal duct empties. Holmes [1] found this opening to be about 6 mm. behind the anterior attached border of the inferior turbinate bone.

EYELIDS

Slight degrees of weakness of the facial muscles should first be looked for. The muscular tone and the lines of expression of one side of the face are compared with those on the other. One should test the power of grimacing, of puckering the lips and of resisting the pulling apart of the tightly closed eyelids. Various degrees of weakness of the facial muscles reduce the power of the winking reflex, the motive power of tear conduction. When such muscular weakness is pronounced, a pool of tears accumulates behind the relaxed lower lid until it spills over onto the face. In such cases the tear sac can readily be irrigated into the nose.

1. Holmes, C. R.: Exirpation of the Lacrymal Gland in Epiphora, Arch. Ophth. **48**:323-333 (July) 1919.

To reduce the incidence, and severity of chronic tearing arising from weakness or paralysis of the facial muscles, adequate and prompt treatment is necessary. The weakness of the facial muscles resulting from peripheral nerve palsy will be discussed first. Then the involvement of the facial muscles which forms a part of a hemiplegia will be considered.

Facial Paralysis of Peripheral Origin.—Proper support of the weakened muscles is essential.[2] This prevents the affected muscles from being overstretched by the sound muscles of the opposite side, with consequent facial disfigurement as well as chronic tearing. This support is given by the early application of two strips of adhesive tape firmly attached to the cheek of the nonparalyzed side, one at the level of the upper, the other at the level of the lower, lip. Thence they are carried across the paralyzed side, to which petrolatum has previously been applied to prevent the adhesive tape from sticking, and the ends are securely fastened to the mastoid process of the paralyzed side. Ectropion is prevented by supporting the paralyzed orbicularis oculi with a sling composed of two narrow strips of adhesive tape. These are fastened to the skin at each end of the eyebrow. Thence they are carried downward and cross each other directly below the middle of the lower lid. Gentle massage is given without removal of the strapping. Soiled adhesive tape may be covered with new strips. Vitamin therapy is prescribed. After one week, exercise of the paralyzed muscles before a mirror is recommended. The strapping is left in place until evidence of return of satisfactory muscular power is obtained. This may require two to twelve weeks. Weak faradic current is used during the third week to increase the tone of the paralyzed muscles. The current used is that needed barely to cause contraction when applied to the normal muscles of the other side of the face. The eye is protected with colored glasses furnished with side pieces.

If after persistent trial such treatment proves of little avail, nerve grafting is advised. As in cases of injury to the facial nerve occasionally occurring with mastoidectomy, grafting the peripheral portion of the damaged nerve to the hypoglossal nerve reinnervates the facial muscles, thus reducing tearing. Nerve grafts which successfully bridge the damaged portion of the facial nerve accomplish the same result. If the affected muscles have undergone too much degeneration, plastic repair with fascia lata slings may be of service.

If the tearing should continue because the lower lid remains slightly relaxed after spontaneous regeneration or after grafting of the facial nerve or use of fascia lata slings, the lid requires tightening to bring it in close relation to the globe. This can be accomplished by the scarring

2. Pickerill, H. P., and Pickerill, C. M.: Early Treatment of Bell's Palsy, Brit. M. J. **2**:457-459 (Oct. 6) 1945.

that follows several electrocoagulating acupunctures along the lower margin of the lid. With topical anesthesia applied to the lower lid, six acupunctures, spaced 4 mm. apart, near the margin of the lid are made with a fine electrode. The current should be strong enough to penetrate the conjunctiva and the tarsus, but not the skin. If more pronounced relaxation of the eyelid has resulted in ectropion, plastic repair is indicated.

Facial Paralysis of Central Origin.—The facial paralysis of central origin forms a part of hemiplegia. When the emergency has passed and the patient begins to convalesce is the time that the facial as well as other affected muscles should be cared for, as outlined for cases of peripheral injury to the facial nerve.

At times after spontaneous recovery from facial paralysis, lacrimation during eating, the so-called crocodile tears, may develop. Spiller [3] suggested that the phenomenon was due to regeneration of nerve fibers which are misdirected, and so fail to connect with the muscles previously supplied. Ford [4] outlined the possible pathway which these fibers assume. Gottersfeld and Leavitt [5] anesthetized such misdirected regenerating nerve fibers by cocainization of the sphenopalatine ganglion. A cotton-tipped probe covered with cocaine paste is held for a few minutes just behind the posterior tip of the middle turbinate bone of the affected side. If this procedure proves effective in temporarily stopping the epiphora, 2 per cent procaine hydrochloride, followed by absolute alcohol injected by way of the posterior palatine foramen, will give more lasting relief. Reinjection is recommended should symptoms recur.

Injury to the lid margin may result in formation of a notch through which tears flow onto the face. Such a notch should be repaired by plastic operation. If such an injury is traumatic or occurs after the removal of a chalazion near the intermarginal space,[6] as it does occasionally, the edges of the lacerated lid margin should be accurately sewed together without delay.

Eversion of the lower lid which permits tears to overflow onto the face, may be caused by cicatrix following trauma. Thorough and persistent massage may bring relief. Otherwise, a plastic operation will correct the eversion and the tearing. Chronic blepharitis with extensive

3. Spiller, W. G.: Contracture Occurring in Partial Recovery from Paralysis of the Facial Nerve and Other Nerves, Arch. Neurol. & Psychiat. **1**:564-566 (May) 1919.

4. Ford, F. R.: Paroxysmal Lacrimation During Eating as a Sequel of Facial Palsy, Arch. Neurol. & Psychiat. **29**:1279-1288 (June) 1933.

5. Gottersfeld, B. H., and Leavitt, F. H.: Crocodile Tears Treated by Injection of the Sphenopalatine Ganglion, Arch. Neurol. & Psychiat. **47**:314-315 (Feb.) 1942.

6. MacMillan, J. A.: Prevention and Treatment of Lacrimation, Canad. M. A. J. **44**:284-288 (March) 1941.

conjunctival hypertrophy or any tumor originating on the conjunctival surface of the lid may produce mechanical ectropion. The use of a 2 per cent solution of silver nitrate, as well as electrocoagulation, will prove of value here. In the aged, relaxation of the muscles of the lower lid is a frequent cause of chronic tearing. A bandage worn at night to support the relaxed muscles is of advantage. Persistent, firm but gentle massage may replace the everted punctum, so that it contacts the lacus lacrimalis. When this method is not successful, the relaxed lower lid, as well as the punctum, can be drawn backward to bring it in close relation to the globe. This is done, as described before, by the scarring which follows several shallow electrocoagulating punctures of the conjunctiva just posterior to the margin of the lid. Severe eversion should be reduced by plastic excision of the redundant tissue. Tumors and other lesions involving the margin of the eyelid should be removed and the defect caused thereby repaired by sliding a graft from the temple.[7]

To emphasize the importance of looking for slight weakness of the facial muscles as an etiologic factor in chronic tearing, I report the case of C. H. S., a man aged 66, who was referred by Dr. Bernard Samuels in January 1943. His right eye had been tearing for more than five years. The past history was irrelevant except for attacks of hay fever. At the first examination, a drop of 1 per cent fluorescein sodium placed in the left eye was quickly transmitted into the nose, but none of the dye was transmitted in the right eye. The right tear sac was readily irrigated into the nose, small amount of mucus stained with fluorescein being washed out. Weakness of the right side of the face was detected. The patient was advised to massage the weakened muscles in an upward direction several times a day. Since tearing continued after several weeks, the right punctum was slit slightly backwards. The condition remaining the same for some time, I tightened the moderately relaxed right lower lid to bring it into close relation to the globa, by means of six electrocoagulating acupunctures, as described. At the next visit fluorescein was transmitted from the right eye into the nose for the first time. Four weeks after the acupunctures were made the right lower lid had tightened and was in firmer contact with the eyeball than was the lower lid of the left eye. Chronic tearing had ceased. Fluorescein was now transmitted from the right eye into the nose more rapidly than from the left. The patient was informed that it might be necessary to repeat this treatment if tearing should reappear. A letter six months later informed me that he had remained cured of his chronic tearing.

PUNCTA AND CANALICULI

Puncta.—The puncta may be closed, blocked or abnormally placed so that they do not contact the lake of tears at the inner canthus. They may be closed congenitally or by formation of scar tissue. They may be blocked by a foreign body, such as an eyelash or, occasionally, a fungous concretion. More commonly they are blocked by chronic swelling, which usually involves the canaliculi as well. An imperforate punctum,

7. Reese, A. B.: Partial Resection of the Lid and Plastic Repair for Epithelioma and Other Lesions Involving Margin of the Lid, Arch. Ophth. **32**:173-178 (Sept.) 1944.

whether congenital or the result of scarring following injury (mechanical, bacterial, chemical or thermal), should be opened. This can be done with the use of local anesthesia by perforating the closure with a sharp needle while stretching the lower lid laterally for counterpressure to the penetrating needle, as well as to straighten the bend of the canaliculus into which the needle is directed. A no. 2 probe can then be passed into the lower canaliculus. An indwelling horsehair should be kept in place until epithelization is complete.

If the punctum is blocked with a foreign body, this should be removed. The treatment of a punctum blocked by chronic swelling is discussed later in connection with similarly blocked canaliculi, with which they usually coexist.

The lower punctum may be abnormally placed. It may face away from the globe, thus failing to come into contact with the tears. To replace a slightly everted punctum, the patient daily should firmly, but gently, massage the lower lid upward. If after a trial, this proves unsuccessful several light electrocoagulating acupunctures just posterior to the base of the punctum will draw the punctum toward the eyeball when cicatrization is complete.

A more strongly everted punctum may be associated with relaxation of the musculature of the lower lid. Here the relaxed muscles should be tightened, so as to bring the lower lid in close relation to the globe. This is readily accomplished with several electrocoagulating acupunctures placed close to the margin of the lower lid, as previously described under treatment of paresis of the lid. The contraction of the scars so produced tightens the lower lid and simultaneously corrects the position of the strongly everted punctum. Merely slitting such a punctum backward to contact the lacus lacrimalis will not necessarily cure the tearing. This is illustrated in the case previously cited (C. H. S.).

The punctum should be slit backward only as a last resort, and then minimally if the lower lid shows no paresis. If such an incision of the punctum should involve much of the length of the canaliculus, the wide-open gutter thus formed fails to pick up the tears because the capillary action of the punctum is destroyed. When the edges of the cut canaliculus lie close together, repeated cauterizations followed by probing may repair it.[8] Beginning at the inner angle, one should cauterize 1 to 2 mm. and then probe with a no. 1 probe. This procedure is repeated at subsequent sittings until the cut canaliculus is repaired. If the lips of the slit canaliculus are farther apart, a plastic operation may bring the freshened cut edges together.[9] This is followed by probing with a no. 1 probe and the use of an indwelling horsehair, to maintain patency.

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8. Spaeth, E.: The Principles and Practice of Ophthalmic Surgery, Philadelphia, Lea & Febiger, 1941, p. 96.

9. Sattler, C. H.: Haarnaht geschlitzter Tränenkanälchen, Ztschr. f. Augenh. **64**:352 (April) 1928.

If the lower punctum is found to be unusually placed, as in some cases of congenital closure, an indwelling stitch of woman's hair, fixed on a nontraumatic needle, taken through the misplaced punctum and emerging at a point just touching the lake of tears, will form a properly functioning new punctum when epithelization is complete. Comparison with the punctum of the other eye, if normal, will aid in the proper placement of the newly formed punctum.

Scarred Canaliculi.—Canaliculi may be closed by scar tissue or blocked by a foreign body or as a result of chronic swelling. If the canaliculus is closed by scar tissue, a sharp needle can be employed, with use of topical anesthesia, to perforate it. The lower lid is pulled away from the direction of the needle during the perforating. If the canaliculus is scarred in its medial portion, the point of the needle should be pushed until it comes into contact with the bony lacrimal fossa. If the punctum as well as the canaliculus is closed by scar, the point for starting the perforation into the tear sac should be slightly closer to the globe than the original punctum. Comparison with the position of the punctum of the normal eye aids in correct selection of the proper point. A probe can then be carefully passed into the tear sac and thence directed downward into the nasolacrimal duct to feel for possible additional obstruction. Patency is maintained by an indwelling horsehair until epithelization is complete. If, for any reason, the horsehair is removed too soon or if bleeding follows subsequent probing, the horsehair should be reinserted.

Three cases illustrating varying degrees of scarring of the lower canaliculus are described.

The first case is that of Mrs. A. K., aged 52, seen in October 1944. Her right eye had teared for six months. A solution of fluorescein was not transmitted from the right eye into the nose, and irrigation was not possible. With a no. 4 probe a scar was palpable at the medial end of the lower canaliculus of the right eye. This was penetrated, thus allowing free irrigation into the nose. A horsehair was inserted and kept in place for two weeks. A letter from the patient six months later stated that her right eye no longer teared.

The second case is that of Mrs. R. D., aged 53, seen in March 1943, who had tearing of the left eye over four years. The lower canaliculus of the left eye was closed by scar at its medial half. The upper canaliculus allowed irrigation into the nose with difficulty. The upper canaliculus of the left eye was dilated at the second visit, and irrigation into the nose was then easily accomplished. As the patient still complained of tearing, a needle was inserted into the lower canaliculus, penetrating the scar tissue until the bony fossa was palpated. A no. 2 probe could be passed into the tear sac and thence into the nasolacrimal duct. A 27 gage vitallium wire was inserted through the opened lower canaliculus. One end of the wire was formed into a loop to prevent injury to the eye. It was necessary to remove this wire in twenty-four hours because of irritation. Two days later, when the irritation had subsided, a horsehair was inserted into the canaliculus and through the punctured scar after dilation with a no. 3 probe. This horsehair was comfortably retained for two weeks. When the hair was removed, fluorescein was transmitted from the

left eye into the nose. The patient was seen eight months later, at which time fluorescein was transmitted normally into the nose from the left eye.

The third case is that of a man with a completely scarred punctum and canaliculus. M. M., a man aged 79, seen in June 1942, was referred by Dr. A. Kanoff. The patient had had tearing of the left eye for many years and had been treated with repeated probings. The left lower punctum could not be found. The left upper punctum was dilated, permitting irrigation into the nose. As in case 2, the upper canaliculus was patent; yet the passage was not sufficient to prevent tearing. I decided to form a new lower canaliculus. A point was selected on the left lower lid analogous to the position of the lower punctum of the right eye, but slightly closer to the globe. So, with the point of a sharp needle placed at this site, and exerting counterpressure by drawing the lower lid away from the direction of puncture, the needle was passed into the left tear sac until the bony lacrimal fossa was palpated. A thin wire, with the end formed into a loop to avoid injury to the eye, was kept in this puncture for six days. It had to be removed because of its annoyance to the patient, although he was most cooperative. After allowance of three days for the irritation caused by the wire to subside, the puncture wound was probed with no. 1, 2 and 3 probes, and a horsehair was inserted into the newly formed canaliculus. On his next visit, one week later, a drop of fluorescein placed in the left eye appeared in the nose for the first time. Because of the apparent favorable outcome and the presence of coincidental acute rhinitis, the horsehair was removed. Removal proved to have been too soon, for in the following week, when the left canaliculus was probed, there was slight bleeding. The horsehair was therefore replaced. A week later, the hair was removed from the newly formed left lower canaliculus, and irrigation into the nose was easily carried out. On five subsequent visits, the last being October 9, a drop of dye in the left eye quickly appeared in the nose.

Blocked Canaliculi.—Infrequently the canaliculi may be blocked by a foreign body, such as an eyelash or a firm, nontender lump, which on examination and culture may prove to be a fungous concretion.[10] In case of the latter the punctum is often reddened, elevated and bathed in a small amount of mucopus. Rarely is the upper canaliculus so involved. A very small spoon can be used to remove the small particles, resembling grains of sand.

Rarely does such a fungus find its way into the tear sac. Morax[11] reported a case in which the fungus set up a purulent inflammation, which pointed at the third upper molar tooth. Incision and drainage and the use of potassium iodide sufficed to effect a cure.

When the canaliculi are blocked by chronic swelling, the tear sac and nasolacrimal duct are usually similarly blocked, often with the production of secretions, which become infected. The slitlike outlet of the nasolacrimal duct into the nose is surrounded with cavernous tissue,

10. Brinkerhoff, A. J.: Actinomycosis of the Inferior Lacrimal Canaliculus, Am. J. Ophth. **25**:978-981 (Aug.) 1942. Turner, N. H.: Dacryolithiasis with Stricture of the Lacrimal Ducts, Virginia M. Monthly **69**:151-152 (March) 1942.

11. Morax, V.: Sporotrichoses primitive du sac lacrymal, Ann. d'ocul. **144**: 49-53 (Jan.) 1911.

which readily swells in response to an irritating condition, such as chronic rhinitis, sinusitis, spurs or deflections of the nasal septum, nasal polyps, cysts, tumors, scars, an inferior turbinate bone tightly placed against the lateral nasal wall or an allergic irritant. Such irritation obtaining for a long enough period causes the mucous membrane in the area to become so hypertrophic as to shut off proper drainage from the nasolacrimal duct, with resultant tearing.

Such causes of irritation should be removed. When little or no benefit follows proper treatment, Wetzel[12] stresses the importance of tests for syphilis as the cause of the dacryocystitis. Other causes of epiphora often misdiagnosed because of their rarity are early neoplasms,[13] fungous concretions in the tear sac, meningocele, mucocele of the frontal sinus[14] with a fistula at the inner canthus, and ethmoidal mucocele[15] present at the inner canthus. The last-mentioned lesion may be mistaken for an osteoma of the orbit or for a dilated tear sac. It can be differentiated from a dilated tear sac by the fact that it is not tender or elastic to touch and that no fluid can be expressed from it on pressure.

Allergic irritants, which cause sneezing as well as tearing, should be tested for and the allergic condition treated by specific desensitization. If such a regimen should prove ineffective for allergic patients, Negus[16] recommended zinc ionization. In such circumstances, I have found that the electrocoagulating current applied under the mucosa of the inferior turbinate bone is far more effective. As the state of the nasal mucous membrane improves so does that of the conjunctiva, and the tearing ceases.

Incidentally, French workers,[17] as well as the Hilgartners[18] in this country, have used ionization with copper and other metal probes passed into the nasolacrimal duct for the treatment of epiphora. After many

12. Wetzel, J. O.: Dacryocystitis: Part Played by Syphilis in Its Etiology, Am. J. Ophth. **28**:511-516 (May) 1945.

13. Spratt, C. N.: Primary Carcinoma of the Lacrimal Sac, Arch. Ophth. **18**:267-273 (Aug.) 1937. Penruan, G. G., and Wolff, E.: Primary Tumors of the Lacrimal Sac, Lancet **1**:1325-1328 (June 11) 1938.

14. Cohen, C., and Reinking, F.: Beiträge zur Klinik der orbitalem Komplikationen bei Erkrankungen der Nebenhöhlen der Nase, Beitr. z. Augenh. **78**:1-76 (Feb.) 1911.

15. Henderson, E. E.: The Relation of the Lacrymal Fossa to the Ethmoidal Cells, Ophth. Rev. **30**:352, 1911. McMillan, A. L.: A Case of Ethmoidal Mucocele, ibid. **30**:15, 1911.

16. Negus, V. E.: The Relation of Ophthalmology and Rhinology, Brit. J. Ophth. **27**:554-557 (Dec.) 1943.

17. von Tripier, T.; Gorecki, and Lagrange, cited by Fleischer, B., in Elschnig, A.: Handbuch der Augenheilkunde, Berlin, Julius Springer, 1922, vol. 2, p. 1532.

18. Hilgartner, H. L., Jr., and Hilgartner, H. L.: Use of Copper Ionization in Treatment of Chronic Stenosis of the Lacrimal Duct, Am. J. Ophth. **18**:54 (Jan.) 1935.

attempts with this modality so applied, I have abandoned it as of too little value. As will be described later, such treatment in the nasolacrimal duct is applied to an effect, not to its cause, which lies in the nasal air sinuses.

Although chronic tearing due to a reflex neurosis from the nose is not included in the category of chronic lacrimation discussed in this paper, it is of interest to note that Negus [16] applied cocaine paste to the sphenopalatine ganglion, behind the posterior tip of the middle turbinate bone. If this stops the tearing temporarily, procaine hydrochloride followed by alcohol can be injected through the posterior palatine canal into the ganglion for more prolonged cessation of tearing.

The mucous membrane walls of the tear sac normally lie in contact when the eye is at rest. This membrane continues downward, forming the lining and the valves of the nasolacrimal duct. Rich venous plexuses underlie this lining membrane, which gradually assumes the characteristics of nasal mucosa as it approaches the nasal cavity. This nasolacrimal membrane shares in the degree of atrophy or hyperthrophy [19] of the nasal mucosa. Inflammation of the nasal mucosa around the outlet of the duct blocks it and causes similar inflammatory changes in the contiguous nasal duct and tear sac. Palpation of the tear sac and comparison with the sac on the opposite side reflect accurately the condition of the nasal mucous membrane. Since most of this tissue is contained within a bony canal, the inflammatory swelling readily obliterates the lumen. Probing [20] of the nasal duct in such cases is of little value and may cause trauma which may result in stricture. A stagnant fluid with mucus, and often pus, accumulates in the sac, forcing apart its walls.

Whitnall [21] reported that in 54 per cent of the 100 European skulls he examined the anterior ethmoidal cells extended as far as the anterior margin of the lacrimal groove. Pus arising from suppurative ethmoiditis may spread through the thin lacrimal bone into the lacrimal groove, pointing externally at the inner canthus. A subacute or chronic inflammatory condition of the anterior ethmoidal cells may similarly extend through the lacrimal bone, producing local periostitis [14] of the lacrimal groove, with swelling at the inner canthus and of the eyelids, so blocking the sac, the canaliculi and the puncta. Moreover, the close anastomosis existing between the venous and the lymphatic plexuses of the

19. Whitnall, S. E.: Anatomy of the Human Orbit and Accessory Organs of Vision, London, Oxford University Press, 1932, p. 244.

20. Tooke, F. T.: Extirpation of Chronically Inflamed Tear Sacs, Montreal M. J. **35**:336-341 (May) 1906. Worth, in discussion on Pollock, W. B. T.: The Treatment of Chronic Dacyocystitis, Lancet **2**:455 (Aug. 12) 1911. Fergus, E. F.: Treatment of Lacrymal Suppurative Disease, Ophth. Rev. **30**:231-239, 1911.

21. Whitnall, S. E.: The Relations of the Lacrimal Fossa to the Ethmoidal Cells, Ophth. Rev. **30**:321-325, 1911.

ethmoid and maxillary sinuses and the mucous membrane lining of the lacrimal drainage apparatus would appear to render the latter susceptible to inflammatory lesions of these sinuses.

In cases of canaliculi blocked by swelling, usually associated with similar blockage of the nasolacrimal duct, conservative treatment should be begun early. The earlier it is begun, the better the prognosis. The puncta and canaliculi are dilated, followed with repeated irrigations of the tear sac with astringent, antiseptic solutions containing added epinephrine hydrochloride and/or ephedrine sulfate. Sulfonamide compounds, antibiotic solutions or similar agents, and other substances dissolved or suspended in fats, oils and waxes may be instilled into the tear sac for longer action. Such treatment was given at weekly intervals in the office in conjunction with displacement therapy for the concomitant chronic nasal sinusitis. For home treatment, the patient was instructed how to empty the tear sac and how to massage it lightly twice daily. While he is in the recumbent position, he instils a drop of an astringent, antiseptic solution into the eye, both before and after emptying the sac. While he is in this position, the head is turned with the affected side down and held lower than the rest of the body while a few drops of a nasal vasoconstrictor are instilled into each nostril.

In more resistant cases the application of 5 per cent silver nitrate around the nasal orifice with retrograde passage into the nasolacrimal duct is useful. The tip of a nasal applicator is tightly wound with a small piece of absorbent cotton, and the end is so bent at a right angle that it will reach as high up into the duct as possible. As stated previously, in 50 specimens, Holmes [1] found that the orifice of the nasolacrimal duct was at an average distance of 6 mm. behind the anterior attached margin of the inferior turbinate bone. If the anterior end of the inferior turbinate bone is tightly placed against the lateral nasal wall, it should be fractured toward the midline, with the use of local anesthesia. Chronic swelling and moderate hypertrophy of the mucous membrane may be reduced by injecting sclerosing solutions [22] under the mucosa. I prefer the use of the better controlled electrocoagulating current, which can deal adequately, in addition, with the greatly hypertrophied mucous membrane, polyps, scars and other tumors.

Because chronic tearing caused by blockage due to swelling in the puncta and canaliculi, as well as in the nasolacrimal duct, is frequently seen, 6 cases will be cited.

Miss F. M., aged 48 was seen in February 1946. The left eye had been tearing for the past six months. The left lower punctum and canaliculus were tightly swollen, but after dilation an unusually large amount of mucopus was washed into the nose with irrigation. There was a high deflection of the nasal septum to the

22. Tremble, G. E.: Epiphora of Nasal Origin, Arch. Otolaryng. **40**:494-496 (Dec.) 1944.

left, with chronic ethmoiditis on that side. Office treatment was given once a week, and home treatment was carried out by the patient twice daily, as previously described. The discharge irrigated from the left tear sac was less on the third visit and continued to decrease on subsequent visits. On the sixth visit, the patient stated that tearing had ceased. A drop of fluorescein was rapidly transmitted from the left eye into the nose. She was advised that a severe head cold might undo the benefit she had received and that, if this should occur, an intranasal operation to improve the drainage of the left ethmoid cells was advised. In May she contracted such a cold. Despite this, the tear conduction apparatus of the left eye continued to function normally, as it had when I last heard from her, in August 1946.

Mrs. S. M., aged 44, was referred by the late Dr. M. Schoenberg in April 1943. Her left eye had teared for two years, for which she had previously been treated. The upper and lower puncta and canaliculi of the left eye were swollen tight. These were dilated, allowing free irrigation into the nose. There was chronic catarrhal involvement of the left ethmoid cells. Treatment was carried out in the office and at home, as previously described. On her third visit, a drop of fluorescein was transmitted from the left eye into the nose, but somewhat more slowly than from the right eye. On the sixth visit, in June 1943, fluorescein was transmitted from the left eye into the nose more rapidly than from the right eye.

Mrs. V. L., aged 43, who was referred by Dr. A. Levine in April 1945, complained of tearing of both eyes for over ten years, the left eye being more affected than the right. Previous treatment had not been effective. There was a pronounced deflection of the nasal septum to the left, with compensatory enlargement of the right middle turbinate bone. Incidentally, the patient complained of tinnitus of the left ear. The upper and lower puncta and canaliculi of both eyes were tightly swollen. These passages were dilated, allowing irrigation of the tear sacs. Chronic bilateral ethmoiditis was treated by displacement therapy at each weekly visit. Home treatment was ordered. On her third visit, a slight amount of fluorescein was transmitted from each eye into the nose. More dye was transmitted at the next visit. At the fifth, and last, visit the patient stated that her tearing had ceased and that the noise in her left ear was gone. She was told that a severe head cold might cause a recurrence of her symptoms and that in that case an intranasal operation to correct the sinusitis would be necessary. It is now a year and a half since her last treatment, and she has informed me that she has remained cured.

Miss E. S., aged 32, was referred by Dr. J. Schor in October 1944 because of tearing of the right eye for over a year. Fluorescein placed in the right eye was not transmitted into the nose. After dilation of the swollen right lower punctum and canaliculus, fluorescein-stained mucus was washed through into the nose. Chronic nasal sinusitis had been present for many years. The right inferior turbinate bone was placed tight against the lateral nasal wall. A submucous resection of the nasal septum, as well as correction of the malplaced right inferior turbinate bone, was advised. Permission for operation was refused because of her pending marriage, on Christmas Day. A 10 per cent solution of silver nitrate on a cotton-tipped probe, with the end bent at a right angle, was introduced with difficulty between the right inferior turbinate bone and the lateral nasal wall and carried up into the nasolacrimal duct. The usual home treatment was ordered. Two weeks later the tearing of the right eye had diminished. When the patient was seen for the last time, a week before her marriage, tearing in the right eye had entirely ceased, and fluorescein was quickly transmitted from the right eye into the nose. It is nearly two years that her condition has been satisfactory.

N. L., aged 52, referred by Dr. L. Bonfield in June 1945, had had tearing from both eyes for a year and a half, the right eye being affected more than the left.

The upper and lower puncta and canaliculi of both eyes were swollen. After dilation, the left tear sac was irrigated into the nose with difficulty. The right tear sac could not be irrigated. Because the patient lived at a distance, visits were fortnightly. On his third visit, the left tear sac was easily irrigated and the right tear sac could be irrigated for the first time, but with difficulty. This case demonstrates that swelling of the nasolacrimal duct may be so pronounced that several treatments are necessary before small amounts of irrigating solution can be syringed into the nose. Should such a duct be probed prematurely, injury to the swollen mucous membrane may eventuate in scar formation. The right middle turbinate bone was enlarged, causing chronic ethmoiditis on that side. Home treatment was ordered, as previously described. On his sixth visit the patient stated that tearing from both eyes had ceased. A drop of fluorescein was quickly transmitted into the nose from the left eye, and less rapidly from the right eye. Six weeks was allowed to elapse before the next visit, the patient continuing treatment at home. At the expiration of that time the better (left) eye still transmitted the dye normally into the nose, but blocking on the right had recurred. The next two visits showed that the left eye was normal, but the right sac and duct were blocked by a small amount of mucus, which prevented the transmission of fluorescein into the nose. I decided that the enlarged right middle turbinate bone would have to be treated if permanent improvement of the right eye was to be secured. This was done on October 30 with electrocoagulation and compression to about half its original size. After healing, the right eye ceased tearing. Dye was transmitted into the nose normally. When the patient was seen six months later, chronic tearing of both eyes remained cured.

A. T., aged 50, was seen in January 1945 with the complaint of tearing of the left eye for six months and of the right eye for a shorter period. He wore a hearing aid. Nasal polyps had been removed twice previously but again blocked the nose bilaterally. The upper and lower puncta and canaliculi of both eyes were tightly swollen. After dilation of the upper and lower puncta and canaliculi, irrigating fluid could readily be syringed into the nose on both sides. The recurrent polyps were destroyed with electrocoagulation in several sittings. Tearing from both eyes ceased. The patient was advised that if polyps should recur soon allergic treatment, as well as ethmoidectomy, would prove of more lasting value. At the present time there has been no recurrence of tearing.

Having discussed blockage of the tear sac and the nasolacrimal duct by swelling, I shall deal with blockage caused by scar tissue. Finally, the epiphora due to obstruction of that portion of the nose into which the nasolacrimal duct drains will be considered. In order to emphasize the most useful part of this paper, I shall discuss these two conditions in the reverse of the order mentioned.

EPIPHORA DUE TO OBSTRUCTION OF THAT PORTION OF THE NOSE INTO WHICH THE NASOLACRIMAL DUCT DRAINS

Such obstruction may be caused by bony spurs, unusual deflections of the nasal septum, chronic swelling and greatly hypertrophied mucous membrane, polyps, cysts, tumors, scars or foreign bodies, as well as an inferior turbinate bone tightly placed against the lateral nasal wall. To cure the tearing, such an obstruction must be removed. If, in addition,

irreversible changes of the mucous membrane of the tear sac and nasolacrimal duct have occurred, these also must be removed.

Three cases illustrating a few such obstructions and the methods used to remove them, are reported. Home treatment was the same as that given in the preceding group of 6 cases.

Mrs. L. R., aged 56, was seen in September 1945. There had been tearing of both eyes for several years, the right eye being affected more than the left, and chronic irritation around the right lateral canthus for several months. She had been treated for the past four months, without relief. The chronic tearing of the right eye caused maceration of the skin at the lateral canthus, on which a fungus had grown. This fungus was brought under control. The most important finding was extreme hypertrophy of the mucous membrane of the right inferior turbinate bone, less pronounced on the left side, extending to the posterior tip, thus producing partial blockage of nasal respiration. This hypertrophic mucous membrane was destroyed by electrocoagulation, first on the right side and then, two weeks later, on the left side. Six weeks later, after reaction had subsided, the right eye ceased tearing and conducted fluorescein into the nose normally. Tearing of the left eye ceased two weeks later.

The second case is similar to the first, but, in addition, an inferior turbinate bone, tightly placed against the lateral nasal wall, was fractured toward the midline. H. G., aged 68, was seen in November 1943. Both eyes had been tearing for five years, the left being affected more than the right. The upper and lower puncta of both eyes were extremely tight, especially those of the left eye. After dilation of the puncta irrigation with saline solution resulted in some mucus being washed into the nose. Twenty-five years before a submucous resection of the nasal septum had been performed. A large septal perforation and extreme hypertrophy of the mucous membrane of the inferior turbinate bones were observed. The degenerated tissue was destroyed by electrocoagulation in five fortnightly treatments. The right inferior turbinate bone, which was tightly placed against the lateral nasal wall, was fractured toward the midline. When the patient was observed on Feb. 29, 1944, both eyes transmitted fluid normally into the nose. Since then he has informed me that his tearing has remained under control.

Mrs. A. K., aged 50, was seen in June 1945. The left tear sac had been excised in 1935. Tearing from the right eye had annoyed her for over one year. Both inferior turbinate bones were atrophic. The upper and lower canaliculi of the right eye were open, but no fluorescein was transmitted into the nose. By irrigation a small amount of solution was forced into the nose. When the patient was seen two weeks later, although no dye was transmitted from the eye into the nose, irrigation through the right lower canaliculus was easily performed, as it was at the next fortnightly visit. Careful reexamination disclosed a large scar extending from the lateral surface of the inferior turbinate bone to the lateral wall of the nose. This was cut through with the electrocoagulating current. Six weeks was permitted to elapse, by which time the reaction had subsided and tearing had ceased. Fluorescein in the right eye was quickly transmitted into the nose. The satisfactory condition continues at the time of writing.

REMOVAL OF SCAR TISSUE IN THE TEAR SAC AND NASOLACRIMAL DUCT

Attempts to remove obstructing scar tissue in the tear sac and nasolacrimal duct have been described by Peters in 1910 and by Dean in

1929.[23] Schuster [24] (1915) described Peters' method as one of slitting the upper and lower canaliculi and perforating the stricture by constant turning of a blunted knife. If after several days the purulent secretion remains, the wound is reopened and the procedure repeated several times, if necessary. Schuster claimed a cure in 77 per cent of the cases. The failures, he stated, were perhaps due to disease of the accessory sinuses of the nose. In order to avoid failure, he stated, one should perhaps first treat the nasal sinusitis before resorting to operations on the tear sac.

Dean avoided the slitting of the canaliculi by direct incision through the skin into the tear sac. He then inserted a thick probe through the open tear sac and stretched the obstructing scar tissue until it was perforated and so dilated that an indwelling silver tube could be inserted. He found practically all the obstructions of scar tissue at the neck of the tear sac. Silver styles had to be worn for a long time, with periodic readjustments and cleaning.

USE OF DIATHERMY IN REMOVAL OF OBSTRUCTION IN THE NASOLACRIMAL DUCT

Worms and Filliozat,[25] as well as Defoug,[26] in 1931, followed the same procedure as did some urologists in combating stricture of the urethra by utilizing medical diathermy to disinfect as well as to restore the caliber of the urethra. Several treatments were given without the use of any local anesthetic so that the current could be regulated according to the sensation of the patient. Defoug conjectured that diathermic coagulation might prove to be the treatment of choice in cases of synechia and of stenosis of the lacrimal passages. M. Fage, in discussion on Defoug's paper, pleaded for a wider use of this modality by ophthalmologists.

In 1933 Spinelli [27] utilized rubber-insulated electrodes passed through an external incision of the skin into the nasolacrimal duct to cut through obstruction. A rubber tube was inserted through the opened obstruction and kept in place for twelve days.

With the area under local anesthesia, Weekers [28] used surgical diathermy with rubber-insulated Galezowski probes nos. 8 and 9, employ-

23. Dean, F. W.: Stenosis of Lacrimal Ducts, Arch. Ophth. **2**:164-168 (April) 1929.

24. Schuster, K.: Zur Geschichte und Kritik der neueren Behandlungsmethoden der Trämensackeiterung, Klin. Monatsbl. f. Augenh. **55**:596-611, 1915.

25. Worms, G., and Filliozat: La diathermie des voies lacrymales, Bull. Soc. d'opht. de Paris, March 1931, pp. 129-131.

26. Defoug: La diathermie dans le traitment del'oblitération des voies lacrymales, Bull. et mém. Soc. franç. d'opht. **44**:264-269, 1931.

27. Spinelli, F.: Diathermische Rekanalization des Tränennasenkanals, Klin. Monatsbl. f. Augenh. **91**:202-207 (Aug.) 1933.

28. Weekers, L.: Rétablissment de la perméabilité des voies lacrymalis, Bull. Soc. belge d'opht., 1932, no. 65, pp. 65-69.

ing a current of 700 milliamperes for two or three seconds. He stated that it is of course preferable to restore the structure and function of the lacrimal apparatus, rather than to detour the tears above the obstruction through an artificial opening made into the nose. The fact that three years later Weekers [29] published a modification to facilitate the surgical technic of the dacryocystorhinostomy of DuBois, Depuy-Dutemps and Bourguet indicates that his results were not satisfactory. This, I believe, was due principally to the improper selection and preparation of cases, and possibly the use of too strong a current. In dealing with a chronic infection of the tear sac with sticky mucopus, for example, removal of the scar tissue by destroying it with electrocoagulation may not be sufficient to cure the condition. This is likely to be the case unless by good fortune the diathermic current should have such a beneficent action on the chronically infected mucous membrane that it reduces the infected secretion and renders it fluid, so that it can drain into the nose. There are cases of sticky mucopus in which complete stricture does not exist, as is proved when strong pressure over the sac forces this viscid secretion into the nose. Nevertheless, such secretion cannot drain spontaneously into the nose.

Preliminary treatment with antiseptic, astringent solutions, sulfonamide or antibiotic preparations or medical diathermy must first be used to control the infection in the tear sac before the obstruction in the nasolacrimal duct is destroyed by electrocoagulation. As stated, if this is not done, despite the removal of the obstruction, the mucopurulent secretion is so viscid that it cannot drain through the fully opened nasolacrimal duct. It is essential therefore to give preliminary treatment to such an infection of the tear sac, as well as to the concomitant nasal sinusitis, before reopening a nasolacrimal duct closed by scar tissue. Such a procedure is likewise of advantage before performing intranasal drainage for cure of chronic infection of the tear sac, but by no means as essential. There, the wide opening of the tear sac and the electrocoagulation of its mucous membrane are adequate to drain even viscid secretion. The chronic sinusitis that is often present is alleviated by the simultaneous removal of the anterior tip of the middle turbinate bone, which is often done as part of the operation.

The method that I have followed in the removal of scar tissue in the tear sac and nasolacrimal duct inconveniences the patient so little that one is tempted to try it in many cases of infection of the tear sac. When advanced age or other conditions contraindicate surgical treatment, it is preferable to bring the infection under control as described and then remove the obstruction by electrocoagulation. If after a reasonable

29. Weekers, L.: Un procedé opératoire aisé et sûr de dacryocystorhinostomie, Arch. d'opht. **52**:241-246 (April) 1935.

length of time tearing persists, intranasal drainage of the tear sac should be performed. A dilated tear sac full of sticky mucopus is best treated with intranasal drainage. I believe it is not worth while trying to cure such a condition by first combating the infection and then removing any obstruction of scar tissue, except when operation is contraindicated.

My experience [30] with transcanalicular incision aided by diathermy to open fully the tear sac in the intranasal operation for cure of infection of the tear sac helped me, similarly, to remove obstruction at the neck of the tear sac, as well as in the nasolacrimal duct. The same insulated electrodes can be used to open the tear sac fully, to combat threatened obstruction at the intranasal opening, to reopen such a closure occurring after any operative method formerly attempted and to destroy obstruction at any spot in or along the entire length of the nasolacrimal duct. The end of the electrode is bent at a right angle to fit the concavity of the eye socket. Electric insulating varnish is applied and baked on until hard. The ends are scraped free of the insulation.

It has been shown by Stevenson,[32] Dean [23] and others that except in congenital cases, the site of the obstruction which blocks normal conduction of tears is generally at the neck of the sac. In beginning the treatment for chronic tearing, conservative measures should be used until all abnormalities of the eyelids, puncta and canaliculi and that portion of the nose into which the nasolacrimal duct drains have first been corrected. If, after this has been done, irrigating fluid does not enter the nose after repeated trials at various sittings, one should palpate with a no. 2 or no. 3 probe for obstruction of the sac or duct. Unless care is exercised, since the bony canal is seldom straight, the swollen mucous membrane is liable to injury when the practically straight probe is pushed against it. The cautious approach here outlined will minimize such injury.

When scar tissue is palpated, usually at the neck of the sac, procaine hydrochloride, injected through a fine hypodermic needle, can be used to anesthetize the sac. At the same time the needle can be passed vertically downward into the sac, where it palpates the obstructing scar. By perforating the scar, thus allowing the solution to be syringed into the nose, one can accurately gage the thickness and toughness of the scar. In cases of traumatic origin, the entire length of the nasolacrimal duct may be filled with scar tissue. This will prevent the flow of procaine solution into the nose unless an exceptionally long needle is used to penetrate it.

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30. Morgenstern, D. J.: Intranasal Drainage for Cure of Chronic Infection of the Tear Sac: Initial Transcanalicular Inverted U-Shaped Incision to Facilitate Full Opening of the Tear Sac, Arch. Ophth. **32**:101-103 (Aug.) 1944.

31. Footnote deleted by the author.

32. Stevenson, M. D.: The Treatment of Lacrimal Obstruction, J. A. M. A. **49**:114-119 (July 13) 1907.

Two cases are reported in which treatment by diathermic rechanneling of the nasolacrimal duct closed by scar tissue was employed with success. In the first the tear sac was blocked by scar tissue at the neck of the sac; in the second the entire nasolacrimal duct was filled with scar tissue as a result of trauma.

Mrs. M. H., aged 58, was seen in March 1944. Both eyes had been tearing for six years, the right being first affected and soon thereafter the left. The left eye had been cured in Munich, Germany, but the right eye continued to tear. In this country she had continued treatment, without success. The right lower canaliculus had been slit. No pus could be expressed or irrigated from the right tear sac. Probing disclosed narrowing of the medial end of the right lower canaliculus and a fibrous obstruction at the neck of the tear sac. The nasal septum was conspicuously deviated to the right above; the inferior turbinate bone was atrophic. A 2 per cent solution of tetracaine hydrochloride was applied to the punctum. The right lower canaliculus was dilated to admit a no. 6 probe. A few drops of 2 per cent tetracaine hydrochloride were instilled into the tear sac. A sheet of composition metal was placed in firm contact with the patient's back to serve as the indifferent electrode. The caliber of the bent end of the insulated electrode was that of a no. 4 probe. This electrode was inserted through the dilated lower canaliculus into the tear sac. The handle of the electrode was directed horizontally away from the eye and supported so that the active tip within the sac was in firm contact with the fibrous obstruction at the neck of the sac. The amount of current used was about 1,000 milliamperes of coagulating current when short circuited. This is equivalent to about 125 milliamperes with the patient in the circuit. As soon as the current was turned on, the obstructing scar tissue gave way as the electrode readily passed vertically down the nasolacrimal duct. There was practically no reaction and no pain. When the patient returned in two weeks, a drop of fluorescein in the right eye was quickly transmitted into the nose. The patient's right eye has since continued to function normally.

Although I did not use injection of procaine hydrochloride in this case, or in the following one, I recommend its use. The purpose is primarily to perforate the obstructing scar with the needle. It thus allows the solution to be syringed into the nose, giving the operator accurate knowledge of the thickness, as well as the toughness, of the scar.

Mr. W. A., aged 67, was seen in May 1945. A fall on the sidewalk six years before had resulted in fracture of his nose, after which a purulent infection of the right tear sac set in. Painful probing had been attempted previously on several occasions, without success. In view of the patient's age and the fact that fracture results in formation of sclerotic bone, which is not easy to fenestrate, I decided first to control the infection and then to reopen the closed nasolacrimal duct. Solutions of sulfonamide drugs and of penicillin were used once a week to irrigate the tear sac, which contained only a moderate amount of infected matter. Eye drops containing a sulfonamide drug were prescribed for home use. After several weeks the tear sac was practically free of infected material. The right lower canaliculus was dilated. A 2 per cent solution of tetracaine hydrochloride was instilled into the tear sac and the active tip of the electrode placed in firm contact with the fibrous tissue blocking the neck of the sac. When the current was turned on, this scar tissue was cut through, but further resistance was encountered. With the current turned on again, the resistant scar was coagulated until the entire length

of the nasolacrimal duct, which was completely filled with scar tissue, was perforated. There was little reaction, the patient being able to return to work the afternoon of the same day. The tear sac was readily irrigated, and a no. 6 probe was passed into the nose once a week for several weeks thereafter. If any tendency to formation of scar tissue palpable with the probe should appear, the spot could be touched lightly with the coagulating electrode. It is now over a year and a half since the patient was cured, and there has been no recurrence.

In the method described, the use of styles is unnecessary. This may perhaps be explained as follows: Nature resents a surgical opening made through cranial bone, such as an opening into the antrum, an opening through the bony lacrimal fossa or the opening of a congenital bony occlusion of the choana,[33] and attempts to close it. Diathermy helps appreciably to reduce this tendency. In contrast to this, scar tissue obstructing the nasolacrimal duct does not show such a strong tendency to closure when opened by diathermic coagulation.

Retrograde insertion of an electrode via the ostium of the nasolacrimal duct in order to reach the obstruction at the neck of the sac, rather than the transcanalicular approach, would offer a great advantage if it were possible. The soft tissues of the canaliculi react to injury, mechanical or thermal, with swelling and possible fibrosis far more readily than do the tissues within the bony nasolacrimal duct. For this reason, it is wiser to use less current at the start. If the strength is insufficient, it can easily be increased. Unfortunately, the anatomic configuration makes the retrograde approach extremely difficult; if not impossible.

The method described in these 2 cases will find its greatest value in that small percentage of cases of congenital dacryocystitis which cannot be cured with conservative measures. In the congenital cases the block is at the lower end of the tear duct, in contradistinction to the acquired cases, in which the block is usually at the neck of the sac. In the conservative treatment of congenital dacryocystitis, Judge[34] advocated removal of a mass of cellular debris blocking the lower end of the nasolacrimal duct by using a cotton-tipped applicator introduced along the floor of the nose and withdrawing it just under the inferior turbinate bone. Should this procedure fail, repeated pressure with the finger over the tear sac blocking the canaliculi will open the blocked duct by hydrostatic pressure in two thirds of the cases. Antiseptic, astringent solutions are used in conjunction with this technic.

I modified this technic in the case of C. R. W., a girl aged 4 months, who was referred by Dr. L. Feit in August 1946. The right eye had been red and had

33. Morgenstern, D. J.: Congenital Atresia of the Postnasal Orifices: A Simple, Effective Office Technic for Treatment by Electro-Coagulation, Arch. Otolaryng. **31**:653-662 (April) 1940.

34. Judge, H. V.: Dacryocystitis of the New Born, New York State J. Med **41**:25-29 (Jan. 1) 1941.

discharged pus since birth. Examination showed that the nose was clean and open. The right inferior meatus was anesthetized with a small amount of 2 per cent cocaine hydrochloride to which epinephrine hydrochloride was added. The end of a fine, cotton-tipped probe was bent at a right angle to fit under the right inferior turbinate bone and to reach the orifice of the nasolacrimal duct. In that area an abnormal, hard mound, projecting downward, was palpated with the tip of the probe. No cellular debris was found on withdrawing the probe. For this reason, a small amount of 0.5 per cent silver nitrate was applied to the area of the orifice with the same cotton-tipped probe. In addition, the mother was instructed how to exert pressure over the tear sac and to use astringent eye drops in conjunction with this technic. When I saw the referring physician in October 1946, he informed me that the baby's right eye had quickly cleared up.

To evaluate properly the efficacy of the intranasal procedure described, no other treatment should be used in conjunction with it; or it should be used in cases in which former conservative treatment has proved ineffective.

In the one third of the cases in which cure is not effected with these conservative means, Riser [35] advised waiting three and a half months before probing with a no. 2 probe. With these combined methods he obtained cures in 97 per cent of cases. Gifford [36] advised a waiting period of six months, with conservative treatment, before probing with a no. 1 probe in the cases in which such treatment was not successful. The probing should be followed immediately by irrigation with isotonic solution of sodium chloride, with the child still under general anesthesia, the head being held vertically upright and bent slightly forward to allow the irrigating fluid to run out through the nose.

There is a striking difference between the prognosis in cases of congenital dacryocystitis and that in cases of the acquired chronic type, in which conservative treatment is successful in about 50 per cent.[35] In all the cases in which conservative treatment fails, operation on the lacrimal drainage apparatus is required to effect a cure. An infant or child is not a proper subject for such a surgical procedure. The child therefore suffers physical as well as psychic irritation from this cause for many years. In the small percentage of congenital cases in which cure is not effected with conservative measures, the ideal method is the electrocoagulation of the blocked lower end of the nasolacrimal duct by means of an insulated electrode, with the use of chloroform anesthesia. This can be done with accuracy from above via the canaliculus, as described. By the retrograde approach, from below, the obstruction could be destroyed with less accuracy, but with a greater margin of safety to the canaliculus if an excessive amount of current should accidentally be used.

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35. Riser, R. C.: Dacryostenosis in Children, Am. J. Ophth. **18**:1116-1122 (Dec.) 1935.

36. Gifford, H., Jr.: Dacryocystitis, Arch. Ophth. **32**:485-487 (Dec.) 1944.

In review, I find that in most of the cases of chronic tearing here reported there was an underlying etiologic factor of chronic nasal sinusitis. Early, conservative treatment of the tear-conducting apparatus and the concomitant nasal sinusitis will usually cure the chronic tearing. Patients who have a recurrence or those who do not adequately respond to such treatment should undergo operation for control of the chronic nasal sinusitis. In addition, it is necessary in those cases in which irreversible reactions of the nasolacrimal mucous membrane have occurred, such as extreme hypertrophy, polypoid degeneration or formation of polyps, cysts or scar tissue, to deal properly with such changes. This can be done in one of two ways, depending on the pathologic changes and the physical condition of the patient. First, a new intranasal opening can be made into the tear sac above the point of blockage, followed by electrocoagulation [37] of the diseased mucous membrane of the tear sac. In the second, and much easier method for the operator and patient, the diseased mucous membrane may be restored after electrocoagulation with an insulated electrode inserted through the canaliculus, as described in the portion of this paper dealing with the destruction of scar tissue which blocks the nasolacrimal duct.

Small [38] stated:

> Delay permits the chronic [nasal sinus] infection to become entrenched and finally irreversible changes take place. Then simple correction of the primary intranasal pathological condition will not necessarily effect a cure of the tearing. In other words, prophylaxis should play a greater role in our treatment of chronic tearing eyes.

This, as has repeatedly been shown, points to the need of close cooperation between the ophthalmologist and the rhinologist in order to secure the best result for the patient.

SUMMARY

Chronic tearing may be caused by slight degrees of facial weakness, which should be looked for first.

Slitting the punctum backward in cases of such tearing is of little value. Tightening the relaxed lower lid, to bring it into close relation with the globe, by means of electrocoagulating acupunctures will cure such chronic tearing.

To reduce the incidence and severity of chronic tearing caused by weakness of facial muscles, prompt and adequate treatment is necessary.

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37. Morgenstern, D. J.: Intranasal Drainage for Cure of Chronic Tear Sac Infection: New Technic Aided by Electro-Coagulation so Simplified as to Be an Office Procedure, Arch. Ophth. **27**:733-745 (April) 1942.

38. Small, C. P.: The Eye, Ear, Nose and Throat, Practical Medicine Series, Chicago, The Year Book Publishers, Inc., 1930, pp. 31-34.

A moderately everted lower punctum is drawn back to contact the lake of tears by placing electrocoagulating acupunctures just posterior to its base.

Abnormalities of the eyelids, as well as methods of their correction, are described.

Abnormalities of the puncta and canaliculi, with methods for their correction, are indicated.

When the canaliculi are blocked by chronic swelling, the tear sac and nasolacrimal duct are usually similarly obstructed. Treatment for the correction of these conditions is outlined.

Treatment for epiphora due to obstruction of that portion of the nose into which the nasolacrimal duct drains is described.

The use of diathermy to remove obstruction in the nasolacrimal duct, usually at the neck of the tear sac, is described.

In that smaller percentage of cases of congenital dacryocystitis with closure of the lower end of the nasolacrimal duct in which conservative measures, including probing, prove unsuccessful, rechannelization by application of the diathermic current is ideal. Cure with this method will save a child many years of physical and psychic irritation.

Most chronic tearing has an underlying etiologic factor of chronic nasal sinusitis.

Delay in treating such infection "permits the chronic infection to become entrenched, and finally irreversible changes take place. Then simple correction of the primary intranasal pathologic condition will not necessarily effect a cure of the tearing. In other words, prophylaxis should play a greater role in our treatment of chronic tearing eyes." [38]

Close cooperation between the ophthalmologist and the rhinologist is necessary in order to secure the best result for the patient.

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THERAPEUTIC SULFADIAZINE POISONING, WITH PEMPHIGOID LESIONS

Conjunctival Changes

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CASES of severe sulfadiazine poisoning have occurred during the course of mass prophylaxis in military personnel, but they have been relatively infrequent. Even these cases ought to be fewer, for the supervising physician has become more aware of the possibility of untoward effects and has trained himself to recognize early the symptoms of idiosyncrasy to sulfadiazine. Serious sulfadiazine poisoning is of three types: that in which the picture of agranulocytosis predominates, that which is associated with urinary suppression and that which presents widespread mucocutaneous pemphigoid lesions. I observed 3 cases of the last type at a Naval training center and found them of special ophthalmologic interest because of the characteristic conjunctival lesions which were exhibited. The systemic reactions varied in these cases, the first patient being moderately ill, the second severely ill and the third critically ill. The severity of the conjunctival lesions paralleled the general clinical course. Because of the rarity of cases of this type, a detailed account of the illnesses follows.

REPORT OF CASES

CASE 1.—*History.*—D. A. J., aged 21, on Dec. 19, 1943 was given 2 tablets (0.5 Gm. each) of sulfadiazine. The medication was repeated daily in the same dose. On December 24 he received his second injection of typhoid vaccine. On December 25 a macular rash appeared on the chest and abdomen. He began to complain of photophobia and ocular pains, and simultaneously his throat became painful. It was thought that he had measles, and he was confined to the sick bay, where more sulfadiazine was given, in doses of 1 Gm. every four hours. The rash became more pronounced, and the entire body became involved. In many areas, particularly the neck, chest and abdomen, "water blisters" appeared. The bullae were preceded by considerable itching. On December 28 the patient was admitted to the hospital.

Physical Examination.—On admission the patient appeared fairly well nourished and mentally oriented. He did not seem to be in great distress. Over his entire body was a red macular rash, discrete for the most part but coalescent in

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some areas. On the neck, chest, abdomen and back were many vesicles, ranging in diameter from 1 to 20 mm. In some regions, particularly the back and the extremities, the lesions were suggestive of measles; in other areas they were of pemphigoid character. The bullae were clear and had an erythematous base. Nikolsky's sign was not elicited. There were foul grayish membranes on the tonsils, palate and posterior pharynx. The conjunctivas were intensely inflamed; there was considerable mucopurulent discharge in the conjunctival fornices, and several small ulcerated spots, covered with the same dirty exudate, were visible on the palpebral conjunctivas.

Therapy.—Treatment consisted in the immediate discontinuation of sulfadiazine, use of mouth washes and gargles of hot saline solution, sedation and application of 3 per cent methylrosaniline chloride U.S.P. to the base of all rupture vesicles. The eyes were cleansed frequently, and antiseptic ointments were applied.

Laboratory Data.—December 28: Culture of material from the throat yielded no hemolytic colonies; green-producing cocci were present.

The sulfonamide level of the blood was 1 mg. or less per hundred cubic centimeters. The solution was too light to read.

December 29: The hemoglobin was 91 per cent; the red cells numbered 4,420,000, and the white cells, 6,950, with 55 polymorphonuclear leukocytes, 36 lymphocytes, 2 mononuclear cells and 7 eosinophils, per hundred cells.

The urine was normal.

Course of Illness.—Jan. 1, 1944: The patient was improving. The mouth was still very sore. Many eroded areas were present when bullae had ruptured. The eyes were red and painful.

January 6: The cutaneous lesions were well healed except for a few crusts on the body and extremities. There was no fever. Persistent sores were present at the angles of the mouth and on the lips.

January 12: One area of erosion on the lip remained. The patient was improving.

The white cell count was 7,150, with 85 per cent polymorphonuclear leukocytes, 13 per cent lymphocytes, 1 per cent eosinophils and 1 per cent band cells.

January 25: Areas which were the sites of previous blisters showed mottling from copper-colored pigmentation. Erythema was still present in other regions. The eyes were still red and sensitive to light.

February 17: The skin was clearing slowly.

May 6: The patient had no complaints. Pigmentary deposits in the skin were still visible.

Ophthalmic Status: Both lids of each eye showed extensive superficial scarring of the conjunctiva. The scars were thin, sheetlike and bluish white. Some were stellate. They contained many newly formed vessels, which for the most part coursed in the same direction as the scar fibers. The scarring was not uniform. The plaques of scar tissue radiated in all directions. The edge of the scars in the lower lids was slightly raised, but no passage could be effected beneath this edge. A few small cysts were visible beneath the scarred surfaces in the upper fornices, just beyond the upper tarsal limits. Several small fan-shaped extensions of the scars passed to the margins of the lids. A small venous varix was present under the conjunctiva of the lower fornix of the right eye.

The patient experienced little discomfort. The eyes did not feel dry, and the normal amount of moisture seemed to be present. The corneas and bulbar conjunctivas were normal.

June 1944: When the patient was last seen, nearly one-half year after the initial complaints, the conjunctival picture had not materially altered.

CASE 2.—A. E. W., aged 19, took sulfadiazine in prophylactic doses of 1 Gm. daily from Feb. 7 until March 5, 1944. On the latter date there developed coryza, soreness of the eyes, mouth and throat and fever. He was admitted to the sick bay with the diagnosis of catarrhal fever and was given additional sulfadiazine in doses of 2 Gm. four times a day. On March 13, the eyes became much more painful, and he noticed a red macular rash on the hands and feet. That evening his mouth became very painful, and he experienced difficulty in swallowing. Administration of sulfadiazine was continued through the evening of March 14, but the symptoms became exacerbated, with balanitis and extension of the rash to the neck and body. His temperature was 100 F. On March 15 he was admitted to the hospital with the suspected diagnosis of measles and Vincent's angina.

Physical Examination.—On admission, the patient was uncomfortable, ill but well oriented. A maculopapular erythema, sparse over the body, but more generalized on the neck, arms and legs, was evident. The lesions varied in diameter from 1 to 6 mm. A few had small vesicular centers. The rash was

Fig. 1 (case 1).—Stellate scarring of conjunctiva of the upper lid. The edges of the scar are undermined.

confluent on the neck, the upper part of the chest, the shoulders and, particularly, the feet. In general appearance it resembled erythema multiforme.

The lids were swollen and red, and the conjunctivas were intensely inflamed. Considerable purulent discharge was present. The bulbar conjunctivas were also greatly reddened. No conjunctival erosions were seen.

The mouth was sore, and the lips were swollen and denuded, with exudate covering the raw areas. Exudate-covered erosions on the palate, uvula and buccal mucosa were noted. The nasal mucosa was red and crusted. The pharynx was relatively clear. The glans penis was eroded and red, with purulent exudate. There was minor generalized lymphadenopathy.

Laboratory Data.—The blood count was normal. The sulfadiazine level of the blood was 10 mg. per hundred cubic centimeters. The urine was normal.

A smear of the conjunctival discharge revealed gram-positive diplococci. Culture of material from the conjunctiva yielded staphylococci and cocci in tetrad formation (probably Micrococcus catarrhalis). The sedimentation rate was 13 mm. in the first hour. The white cells numbered 10,400, with 78 polymorphonuclear leukocytes, 19 lymphocytes and 3 mononuclear cells, per hundred cells.

Course.—March 16: The sulfonamide level of the blood was zero.

Treatment was essentially the same as that in case 1.

March 28: The oral mucosa was still unhealed. The patient was afebrile and felt well.

April 11: The lips had finally healed. The eyes were fairly comfortable.

August 18: A smear of material from the conjunctiva showed few gram-positive diplococci and no pus cells.

September 18: Examination of the lids six months after hospitalization revealed the following condition:

The conjunctiva of the right upper lid contained several large stellate scars. The arrangement of the blood vessels around these scars was interesting. Perhaps a dozen vessels emerged from the deeper layers of the conjunctiva, to surround each scar; they extended inward, giving off small twigs but not quite

Fig. 2 (case 2).—*A*, partial epitarsus of the upper lid of the right eye. A similar epitarsus is present nasally. *B*, extensive scarring of the upper palpebral conjunctiva of the left eye. Small subconjunctival cysts are evident nasally.

reaching the center of the scar. Avascular islands of scar tissue thus appeared to be surrounded with a radiating corona of blood vessels. A partial epitarsus was present (fig. 2*A*). A fold of temporal bulbar conjunctiva extended from the globe to the lid. A shallow conical conjunctival pocket was thus formed, with the mouth opening laterally and the tip of the pocket at the middle of the upper tarsal edge.

The right lower lid appeared normal except for a thin linear scar parallel to its margin.

The left upper lid presented a large smooth scar, extending from the upper tarsal border nearly to the margin of the lid; about one-half the conjunctival surface was occupied by this scar, which was oblong. This area was sparsely

vascularized, a fact readily demonstrated by exerting slight pressure against the everted lid. The remaining conjunctiva was thickened but fairly smooth, and was intensely red. A few fine, faint scars were evident near the margins of the lid. A partial epitarsus, similar in appearance to that of the right lid, was present on the temporal side (fig. 2 *B*).

The left lower lid was much less reddened and contained a narrow linear scar running nearly the entire length of the lid, close to the margin. Near the outer angle was a cyst of a meibomian gland, transparent on transillumination and surrounded by a zone of bluish black pigment. At the nasal portion of the lid, on the conjunctival surface, was a healed ulcer, the base of which was filled with small red follicles.

A slight amount of mucoid secretion was present on all the lids. The patient was well enough for duty, but the eyes were still irritated.

Case 3.—J. L. W., aged 26, took sulfadiazine in prophylactic doses of 1 Gm. daily from Feb. 7 to Feb. 24, 1944. On February 25 he was admitted to the sick bay, complaining of a "cold" and sore eyes. He was treated for incipient measles, with larger, but unrecorded, doses of sulfadiazine. He soon presented severe conjunctivitis, a maculopapular rash on the chest and a morbilliform rash on the feet and body (fig. 3). The throat was congested, with a membrane over the pharynx. Severe stomatitis was present. There were diminished breath sounds over both lungs and rales in the bases of both lungs.

The patient was admitted to the hospital on February 26. His eyes were swollen and red; his lips were excoriated; his throat was inflamed and covered with a dirty white exudate. The gums were edematous and bleeding; the breath was foul. The body was covered with a confluent rash. A diagnosis of malignant measles was made and the patient was given sulfadiazine, 1 Gm. every four hours. On February 27 the temperature rose to 102.4 F. The entire body was covered with the rash, and vesicular and bullous lesions made their appearance. The pemphigus-like blisters were most extensive over the face, chest and back. The condition was recognized as a reaction to sulfadiazine, and administration of the drug was immediately discontinued. A transfusion of 500 cc. of blood was given, and injections of penicillin, 100,000 Oxford units daily, were instituted. Sedatives were prescribed; fluids were forced; cool saline packs were applied to the face, and the bed was liberally powdered.

Course.—February 29: The patient continued to be febrile (102 F.). There was considerable cutaneous discomfort; the eyes were sore, and the mouth was raw. He was almost completely covered with vesicles, and the skin in the vesicular areas was brownish or dusky. The epithelium had stripped off about the lids, leaving large erosions. The conjunctival surfaces of the lids showed erosions which were covered with a dirty exudate. The nasal mucosa was congested, and the lips were swollen. The genitalia were involved. The soles were covered with one massive bulla.

A roentgenogram of the chest revealed nothing significant. The blood count was essentially normal. Rales, due to exudative bronchitis, persisted in both lungs.

March 2: The urine gave a 1 plus reaction for albumin and contained a few red cells.

March 6: Copious yellow exudate was obtained from the mouth and throat. The patient coughed considerably. He complained of retrosternal burning and epigastric pain.

March 7: The condition was somewhat better. The skin showed only a few new vesicles; these were superficial and lay in the uppermost part of the stratum

corneum. The rest of the skin was healing without infection, except for the vermilion border of the lips. The lips were swollen. A red "butterfly" was present over the nose, with broken blisters and sloughed skin. The eyes were slowly improving in appearance. A roentgenogram of the chest revealed a small amount of fluid at the base of the left lung.

March 13: The dose of penicillin was gradually reduced to 25,000 units daily. Considerable postinflammatory pigment was visible in the skin. The mouth

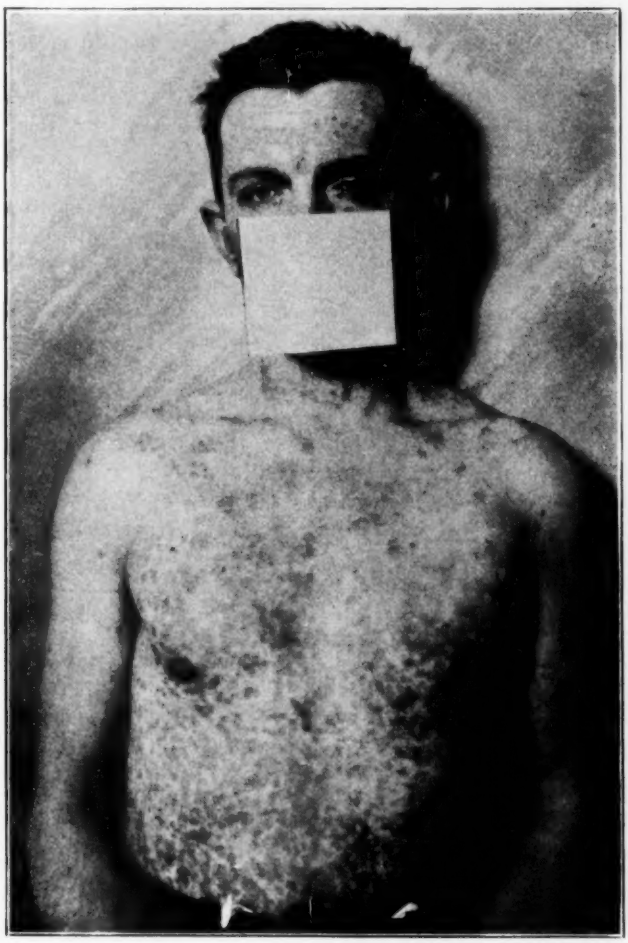


Fig. 3 (case 3).—Diffuse, copper-red mottling of the skin of the face and body. The rash persisted for over a year.

was still raw. The glans penis was denuded, and the scrotum was red and oozing. The lids continued to improve slowly.

March 17: The patient complained of pain in the left calf and along the inner aspect of the thigh, from the popliteal area to Poupart's ligament. There was a sharp rise in temperature.

March 18: Pain was present in the lower part of the abdomen, being due probably to thrombophlebitis at the bifurcation of the inferior vena cava.

March 20: The patient had a sudden onset of severe pain, localized in the left side of chest, in the region of the seventh and eighth ribs near the anterior axillary line. Infarction of the pulmonary artery was suspected.

March 21: A roentgenogram showed the absence of infarct. The fluid was gone. A friction rub was audible. The pain may have been due to pleural roughening, which became evident on resorption of the fluid.

April 6: The patient was doing well. The white cell count was 18,000, with 5 per cent eosinophils.

April 18: There was moderate edema of the left leg and ankle, with pain along the outer aspect of the thigh.

April 27: Redness of the left eye was increased, with edema of the lids.

April 28: There was slight ptosis of the left upper lid. Vision was 20/20 in the right eye and 10/20 in the left eye.

May 2: An ophthalmologic consultation was held. The fundi and corneas were normal. The conjunctivas of both eyes were inflamed and thickened and showed irregular scarring, with contraction of the scar tissue, particularly in the lower fornices. There was a tendency to dryness in the healed areas. A large conjunctival cyst was present in the upper fornix of the left eye and a small cyst in the lower fornix of the right eye. All the lids showed epitarsal adhesions. The conjunctival lesions simulated pemphigus and must be classified as pemphigus-like lesions, part of a generalized reaction to sulfadiazine. The patient complained of tearing. Both lower lids were becoming everted, especially the left. Both lower puncta, particularly that of the left eye, were involved in the process of shrinkage. Fluid passed through both lacrimal canals, but not readily.

June 10: The puncta were difficult to find.

An indolent ulcer had appeared on the anterior aspect of the left tibia.

Ophthalmic status: The conjunctiva of the upper lids had become thickened, velvety and edematous, with multiple small and large cysts (fig. 4 *A*). Two epitarsal membranes formed connections with each lid. These formed two wide pockets, with the respective stomas at the temporal and nasal edges of the lid, and ended near the center of the lid, but were not connected with each other.

The conjunctiva of the lower lids represented a later stage in the healing process. It showed a tendency to dryness on portions of the lids and fornices. Scarring was extensive and passed over to the margins of the lids; at the same time, the epithelium from the lid margin extended in some areas to the conjunctival surface. The bulbar epithelium was puckered with scars. A probe could be passed under the epitarsus in the lower fornix from a nasal opening along the entire length of the lid, but the channel ended blindly at the temporal extremity. An unusual feature was the presence of circular ulcers, ranging in diameter from the size of a pinpoint to about 2 mm. (fig. 4 *B*). They were located chiefly in the scarred area, but were visible in otherwise apparently normal islands of conjunctiva. When seen with the slit lamp, they were startlingly reminiscent of the hole in a grayish detached retina. The edge of the ulcer was undermined in some instances and could be explored with a toothpick to a depth as great as 1 mm. The floor usually contained grayish or yellowish debris. The ulcers at times were covered with a transparent layer of epithelium, beneath which could be seen small yellowish, fatty globules. A similar fatty infiltration was visible on the margins of the lids. The meibomian glands were prone to form serous cysts, which could readily be transilluminated and around which black pigment was deposited. Distichiasis was present.

Application of sulfadiazine powder or ointment to the lids was well tolerated and produced no reaction.

October 1944: When the patient was last seen, eight months after the onset of symptoms, the conjunctival picture had not materially changed. He complained of tearing and moderate irritation of the lids. A slight discharge was noticeable. The pigmentation over the body had begun to fade.

The lower epitarsal membranes had previously been resected, and the larger conjunctival cysts had been removed. Sections of an epitarsal membrane showed

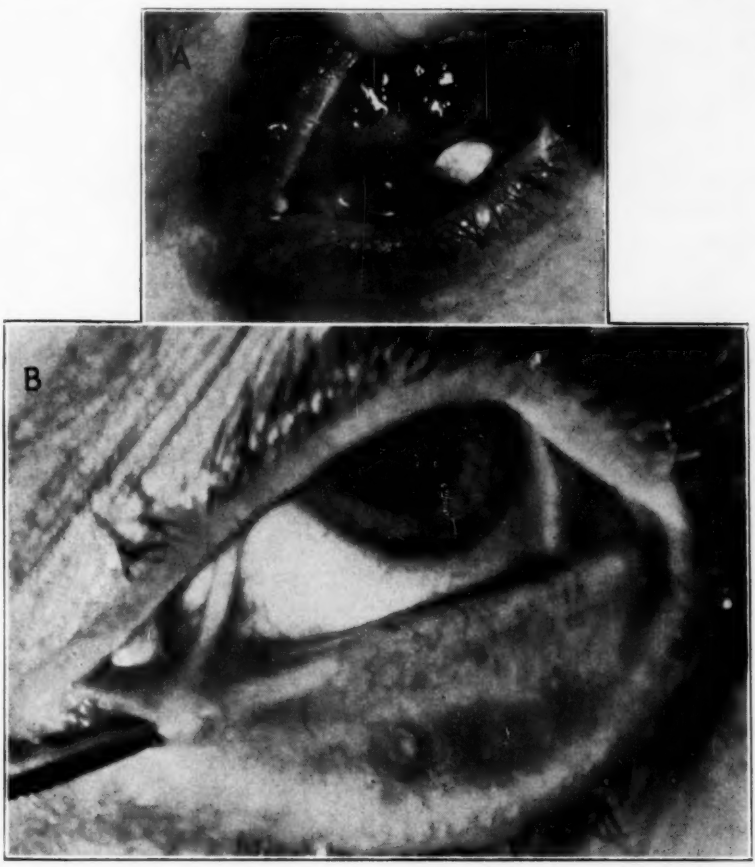


Fig. 4 (case 3).—*A*, multiple cysts of the conjunctiva of the upper lid. The conjunctiva is thickened and velvety. *B*, epitarsus of the lower fornix. Three circular conjunctival ulcers are present on the lower lid. Each is surrounded by a zone of inflammation.

normal conjunctival epithelium in a double fold, with connective tissue filling the space between (fig. 5). A sparse round cell infiltration was present in the connective tissue.

A conjunctival ulcer with the adjacent conjunctiva was excised for pathologic examination. The report, by Col. J. E. Ash, director of the Army Medical Museum, follows.

"Examination disclosed a conjunctival ulcer, the base of which was coated with inflammatory exudate. The margins were widely undermined and epithelized (fig. 6). The local lesion itself was nonspecific. The sequence of events suggests that the integumented interruption was a reaction to sulfadiazine. The persistence of the conjunctival lesion after regression of the cutaneous eruption was probably due to the epithelial downgrowth at the margin of the ulcer."

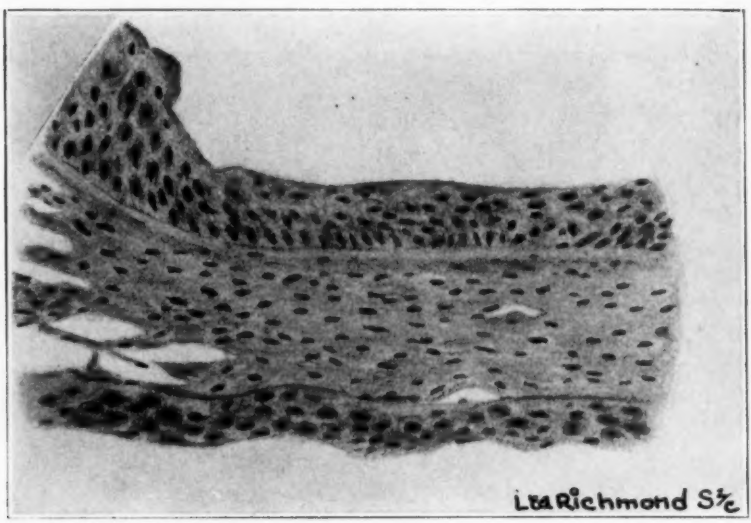


Fig. 5.—Section of the epitarsus. There is a clear basement membrane under one of the epithelial surfaces.

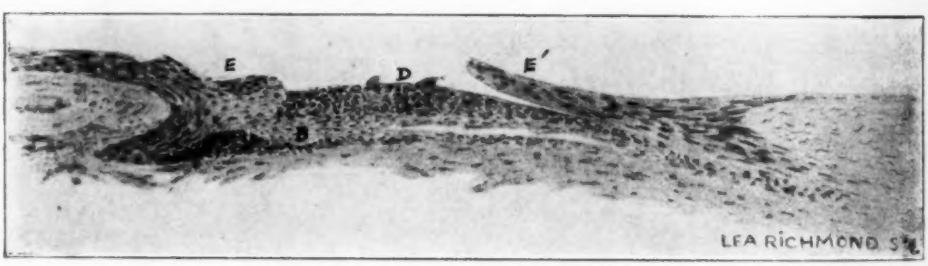


Fig. 6.—Cross section of the conjunctival ulcer. The edges *E* and *E'* are undermined and epithelized. The base of the ulcer contains cellular debris (*D*). The epithelium is attempting to bridge the floor of the ulcer at *B*.

COMMENT

In large military establishments, where contagious diseases are prevalent and the possibility of their appearance is constantly kept in mind, the early evidences of sulfadiazine poisoning may lead to the mistaken diagnosis of scarlet fever or measles. If administration of

sulfadiazine is not discontinued, the reaction may simulate malignant measles or acute pemphigus. The conjunctival lesions in cases of sulfadiazine poisoning consist at first of large ulcerations, conjunctival thickening and formation of cysts, and then of extensive scarring. The edges of the scars are frequently undermined. There are persistent thickening and inflammation of the unscarred epithelium. The initial ulcers heal. Later, small circular ulcers of the palpebral conjunctiva, with undermined epithelized edges, apparently caused by rupture of some of the cysts, may appear and persist for well over half a year. Many of the cysts remain unruptured. Epitarsal membranes on both the upper and the lower lid are a part of this unique picture; their mode of formation is not clear. Tearing may be caused by narrowing, distortion and eversion of the puncta. The cornea is not affected.

In differential diagnosis, one must consider the ectodermosis erosiva pluriorificialis form of erythema multiforme, true pemphigus and measles. A history of ingestion of sulfadiazine is enough to predicate the diagnosis of therapeutic sulfadiazine poisoning; sulfadiazine crystals in the urine and the presence of sulfadiazine in the blood are confirmatory evidence. The ordinary form of erythema multiforme does not leave permanent changes; ectodermosis erosiva pluriorificialis almost invariably involves the cornea. The condition described differs from true pemphigus in the epitarsal membranes and the punched-out conjunctival ulcers; there is not the specific histologic picture observed in cases of true pemphigus. However, in referring to the cutaneous lesions, the dermatologist expressed the following opinion: "This reaction resembles acute pemphigus, supporting the belief that the latter is a toxic process and may be due to drug intoxication."

Treatment must be symptomatic. The general condition of the patient must be supported by blood transfusions, infusions of dextrose and administration of penicillin. The skin must be kept clean and protected. Bland eye washes and ointments help to relieve discomfort. Secondary conjunctivitis may be superimposed, and this is controlled with the usual antiseptic remedies. Large cysts should be excised. Eversion of the lids and stenosis of the puncta must be dealt with surgically.

6 West Seventy-Seventh Street.

SELENIUM BURN OF THE EYE

Report of a Case, with Review of the Literature

J. MYRON MIDDLETON, M.D.
LOS ANGELES

SELENIUM and its compounds are used extensively in the arts and in industry, but relatively little has been reported in this new field.

The element selenium was discovered by Berzelius in 1817; it is intimately related to sulfur, arsenic and tellurium and shares many of their physical and chemical properties. In addition to the element itself, some of the commonly used compounds are: hydrogen selenide; sodium selenide; selenium dioxide; selenium oxychloride; selenious acid and its salts sodium and potassium selenite, and selenic acid and its salt sodium selenate.

The compounds of selenium are used in the manufacture of ruby glass, as well as in decolorizing glass. They find a place in the production of pigments for paint and ink and in coloring plastics. In metallurgy, they are used in the manufacture of stainless steel and copper alloys. They are also used extensively in the rubber industry, in fireproofing of electric cables and in photoelectric equipment. They are used as well in the manufacture of insecticides, general chemicals, cement and lime.

REVIEW OF THE LITERATURE

No case of selenium burns of the eye can be found in the literature. Reports of cutaneous manifestations and generalized intoxication in man are few.

Dudley [1] reported a self-induced, third degree burn of the skin of the forearm with selenium oxychloride, which was slow to heal. The same author demonstrated the vesicant properties of the substance on the skin of rabbits, as well as its extreme general toxicity. Three episodes of finger nail burns, with loss of nail substance, were reported by the patient himself.[2] Pringle [3] reported 5 cases of burns, derma-

1. Dudley, H. C.: Pub. Health Rep. **53**:94, 1938.
2. Personal communication to the author.
3. Pringle, P.: Brit. J. Dermat. **54**:54, 1942.

titis and sensitivity to selenium among industrial workers. He stated that the molten metal apparently produces lesions of less severity than its salts, for the metal burns were primarily thermal. Ellis and associates [4] noted the experimental production of exophthalmos in fish by intraperitoneal injection of sodium selenite—intense edema of the orbital fat resulted.

In the acute form (acquired type) of poisoning, selenium produces "blind staggers" in cattle. In the chronic form of selenosis no ocular involvement is observed. Ophthalmologic observations are few, but Stenn [5] offered an excellent picture of selenosis in the eyes of cattle:

> . . . The eyelids are edematous, and lacrimation is profuse. The aqueous becomes swollen and turbid, and the cornea often shows a hemorrhagic opaque white mass protruding beyond the curvature of the eyeball, making the limbus of the cornea indistinguishable.

GENERAL TOXIC ACTION

Selenium has many toxic effects. It is transmitted through the placenta of poultry.[5] In the progeny of poultry fed diets high in selenium, absence of one or both eyes, cyclops and rudimentary eyes have been reported.

Selenium compounds are extremely lethal, as evidenced by the toxicity of undiluted selenium oxychloride ($SeOCl_2$) [1] which caused the death within twenty hours of rabbits receiving 0.1 cc. of the oxychloride to one area of the skin surface.

Smith and associates [6] showed that the principal concentration of selenium was in the parenchyma, in combination with tissue protein, and that 75 per cent was excreted through the kidneys. Shultz and Lewis [7] reported that 17 to 52 per cent was excreted by the lungs as a volatile compound.

Twomey and Twomey [8] reported cerebellar hemorrhages in ducks fed selenium. Experimentally, in rats, focal necrosis was noted in the liver, hematopoietic system, lungs, kidneys and heart. By con-

4. Ellis, M. M.; Motley, H. L.; Ellis, M. D., and Jones, R. O.: Proc. Soc. Exper. Biol. & Med. **36**:519, 1937.

5. Stenn, F.: "Alkali Disease"—Selenium Poisoning, Arch. Path. **22**:398 (Sept.) 1936.

6. Smith, M. I.; Stohlman, E. F., and Lillie, R. D.: J. Pharmacol. & Exper. Therap. **60**:449, 1937.

7. Schultz, J., and Lewis, H. B.: J. Biol. Chem. **133**:199, 1940.

8. Twomey, A. C., and Twomey, S. J.: Science **83**:470, 1936.

trast, the low concentration in the brain is striking. Uremia and ascites were prominent features. Fitzhugh and associates [9] reported the occurrence of hepatic adenocarcinoma in rats after protracted ingestion of selenium.

Clark [10] stated that selenium resembles sulfur compounds; however, selenium inhibits cellular respiration, whereas sulfur is intimately associated with the discharge of respiratory function. Selenium replaces sulfur in compounds, resulting, for example, in cystine combined with selenium instead of with sulfur. Thus, it creates a sulfur deficiency in animals by replacing the sulfur in cystine and keratin. Selenium exerts an inhibitory effect on enzymes; it may possibly inhibit glycolysis. Amor and Pringle [11] stated that, although in general selenium is chemically similar to sulfur and tellurium, its toxic action resembles that of arsenic. In general it has a toxic action on oxidative processes. It is irritative as well as inhibitory. Tolerance does not develop. Amor stated that selenium poisoning in man resembles pellagra.

Lemley [12] reported cases of selenosis with dermatitis in man and the beneficial effect of bromobenzene. A high protein, low carbohydrate intake was found to protect rats fed diets high in selenium.[13] Rhian and Moxon [14] found arsenic effective in prevention and treatment of selenosis in dogs. Waters and Stock [15] reported the preventive and therapeutic value of 2,3-dimercaptopropanol (BAL) in poisoning with trivalent arsenic, the biochemical mechanisms of which are similar to those of selenium.

The local effects are principally irritative, as evidenced by irritation of the nose and throat, dermatitis and vesication (Dudley,[1] Pringle [3] and others). Selenium salts produced third degree burns of the skin, attended with severe induration, deposits of the element selenium and delayed healing.

REPORT OF CASE

W. A. Z., a chemist aged 36, was accidentally sprayed with selenium dioxide at 9 a. m. on Dec. 13, 1944, sustaining burns of both eyes, the entire face and the

9. Fitzhugh, G. O.; Nelson, A. A., and Bliss, C. I.: J. Pharmacol. & Exper. Therap. **80**:289, 1944.

10. Clark, A.: J. Trop. Med. **43**:250, 1940.

11. Amor, A. J., and Pringle, P.: Bull. Hyg. **20**:239, 1945.

12. Lemley, R. E.: Journal-Lancet **60**:528, 1940.

13. Smith, M. I.: Pub. Health Rep. **54**:31, 1939.

14. Rhian, M., and Moxon, A. L.: J. Pharmacol. & Exper. Therap. **78**:249, 1943.

15. Waters, L. L., and Stock, C.: Science **102**:601, 1945.

back of the neck. He irrigated the parts immediately with tap water and presented himself for treatment in the receiving ward of the Philadelphia General Hospital.

He had a past history of episcleritis and iritis of the left eye in 1942 and of spondylosis chronica ankylopoietica of many years' duration.

When he was seen in the receiving ward of the Philadelphia General Hospital one hour after the accident, burning, pain and lacrimation were severe and spasm was extreme. There was intense injection of the palpebral and bulbar conjunctivas. The corneas and conjunctivas took no stain with fluorescein. There were several old posterior synechias in the left eye, but the pupils were round, regular, equal and active in direct and consensual response. There were first degree burns of the lids, the upper part of the face and the lower part of the neck. The eyes were freely irrigated with isotonic solution of sodium chloride; phenocaine ("holocaine") hydrochloride was instilled, and a bland ointment was applied to the skin of the lids. After this the patient was discharged. Six hours later he returned, complaining of severe, persistent, intolerable pain in both eyes, with lacrimation and photophobia. Grossly, vision was unimpaired.

Examination at that time revealed intense chemosis of the bulbar conjunctiva and beginning marbleization of the lower half of the bulbar conjunctiva, below each cornea. These areas, as well as the lower one fourth to one third of each cornea, stained deeply, with a flat line of demarcation above, corresponding to the line of the upper lid. The patient was then admitted to the Philadelphia General Hospital and placed under treatment with 1 per cent atropine sulfate, "metycaine hydrochloride ophthalmic ointment 4 per cent," and codeine and acetylsalicylic acid as needed. On his admission, 1,500 cc. of isotonic solution of sodium chloride was given intravenously.

Sixteen hours later vision was definitely blurred. There were exaggeration of all symptoms and considerable discharge of thick, white mucoid material at the margins of the lids. Edema of the lids, however, was reduced. The bulbar conjunctivas had progressed to almost complete marbleization, and the lower three fourths of each cornea was dulled. This entire area stained deeply with fluorescein.

Topical application of a solution of penicillin, 500 units per cubic centimeter, was instituted every hour, as well as continuous application to the face of packs saturated with saline solution (use of ointments was discontinued).

On December 14 the patient was seen in consultation by Dr. Alfred Cowan and Dr. Francis Heed Adler, and the following conclusions were reached:

1. It was too late to use 2,3-dimercaptopropanol (BAL).

2. The ophthalmologic prognosis should be guarded because of the extreme ischemia of the bulbar conjunctiva.

3. It was advisable to consider the future necessity of mucous membrane grafts if the corneal slough continued.

On December 15, with the use of anesthesia induced by the intravenous administration of pentothal sodium, a mucous membrane graft, 12 by 8 mm., was applied beneath the limbus of the right eye. The postoperative course was complicated by pulmonary atelectasis, which cleared within twenty-four hours.

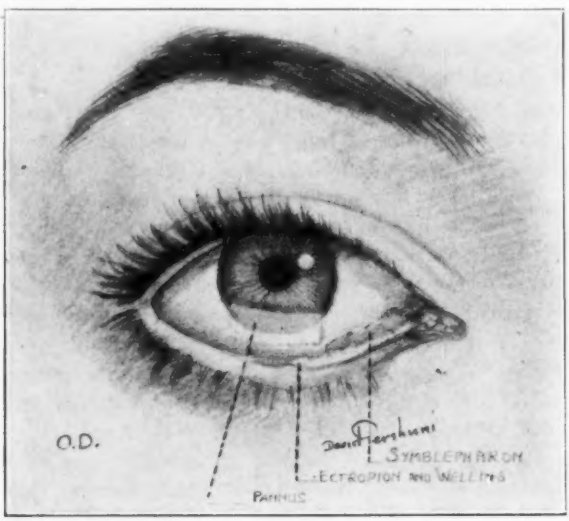
The patient continued to have a slight foreign body sensation. Ulceration appeared slightly deeper. However, the uninvolved areas of the cornea retained normal luster and took no stain with fluorescein.

The conjunctiva of the lower one half of each eye remained marbleized, dull, rough and thickened and stained with fluorescein. A deep ciliary flush appeared at the lower part of the limbus, from 4 to 8 o'clock.

Early adhesions appeared in the lower cul-de-sac and the corneal erosion seemed deeper.

On December 16 the corneas began to clear from above downward. The mucoid discharge was more profuse in the right eye. and adhesions were definitely formed, being most conspicuous near the caruncle. By the following day the upper one half of the right cornea had cleared.

On December 18 the entire right cornea was clear but photophobia was severe. However, the graft was well vascularized and attached, and the right cornea did not stain with fluorescein. Pallor persisted in the lower portion of the bulbar con-



End result of a mucous membrane graft to the right eye in repair of corneal sloughing, which resulted from a selenium burn.

junctiva, being more pronounced in the left (ungrafted eye). The left cornea still stained below.

On December 29, sixteen days after admission, the patient was discharged. Naked vision was 6/9 in the right eye and 6/6 in the left eye. Both eyes were almost completely quiet. Several fine adhesive bands remained in the lower cul-de-sac of the grafted eye. The graft was elevated and produced a moderate degree of ectropion of the lower lid, as well as a partial pannus of the lower one sixth of the cornea.

The patient's subsequent course was unsatisfactory, in that conservative measures, consisting of the use of triglyceride of tannic acid and 2 per cent silver nitrate and massage, failed to flatten the graft, although it lost a degree of lividity.

Fourteen months later, mild ectropion of the right lower lid was observed to persist. Lacrimation was troublesome. The cosmetic appearance of the graft was

unfavorable. Beta roentgen irradiation was decided against, and surgical removal of the graft was planned.

COMMENT

Most selenium compounds are vesicants. They are acid in reaction, and their toxic action on tissue is the same as that of any strong acid, producing severe burns, which are slow to heal.

In the case reported, replacement of the sulfur in keratin by selenium heightened the otherwise simple trauma of a burn. Tissue destruction was not immediately apparent, but it was slowly progressive for several hours and was then demonstrated by staining. The value of any late treatment may be questionable, for the selenium will already have combined with tissue proteins.

In this case, the mucous membrane graft was seemingly not necessary. However, with no previous experience in the treatment of selenium burns and with the severe involvement of both eyes by a chemical of unknown toxic action, it was deemed advisable to resupply corneal nutrition quickly. The grafted eye recovered more promptly, but the graft led to postoperative ectropion, partial symblepharon, astigmatism and an undesirable cosmetic result. (The mucous membrane flap may have been too thick.)

The therapeutic value of 2,3-dimercaptopropanol (BAL) in the acute phase of the disease was considered.

SUMMARY

A case of selenium burn of the eye, together with a review of the literature, is presented. A mucous membrane graft was made, but, in retrospect, the procedure may have been unnecessary. Intravenous administration of fluids was used to combat a possible toxic level of absorption. It was felt that 2,3-dimercaptopropanol (BAL) therapy might have been the ideal method. Complete recovery from acute symptoms occurred within ten days.

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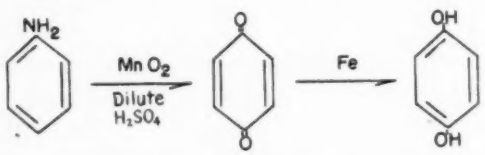
CORNEAL AND CONJUNCTIVAL PIGMENTATION AMONG WORKERS ENGAGED IN MANUFACTURE OF HYDROQUINONE

BANKS ANDERSON, M.D.
DURHAM, N. C.

OCULAR lesions developing in workers exposed to aniline or its derivatives have been previously reported. MacKinley,[1] in 1886, reported brown discoloration of the cornea and conjunctiva in an aniline plant worker with slight reduction in vision. In 1897 Senn[2] observed among 32 workers in aniline dye 18 with sepia brown staining in the interpalpebral zone. In 10 of these workers only the conjunctiva was stained; in 8 the cornea was involved. Senn postulated that this staining was due to the oxidation product of aniline, viz., paraquinone. K. Velhagen Jr.[3] collected a series of 6 cases of workers in hydroquinone plants with lesions of the conjunctiva and cornea of various degrees, similar to those developing in workers described in the present report.

Since the manner in which the persons involved in this study were exposed to the chemical is a problem of industrial hygiene rather than one of ophthalmology, I shall limit myself to a brief description of the chemical reactions which occur in the manufacture of the substance. Quinone in this instance is produced by the oxidation of commercial aniline oil by means of manganese dioxide in the presence of aqueous sulfuric acid. The quinone distilled from this reaction mixture is then reduced to hydroquinone by the addition of iron dust. Disregarding the rather intricate mechanism involved in the oxidation, distillation and reduction of the compound, one may write the equation for the end product as follows:



From the Division of Ophthalmology, Duke University School of Medicine.

1. MacKinley, J. G.: Intense Pigmentation of Corneae and Conjunctiva, Tr. Ophth. Soc. U. Kingdom **6**:144, 1886; cited by Velhagen.[3]

2. Senn, A.: Typische Hornhauterkrankung bei Anilinfärbern, Kor.-bl. f. schweiz. Aerzte, 1897, p. 161; cited by Velhagen.[3]

3. Velhagen, K., Jr.: Chinonverfärbung der Lidspaltenzone als Gewerbekrankheit in der Hydrochinonfabrikation, Klin. Monatsbl. f. Augenh. **86**:739, 1931.

The raw materials from which this chemical is manufactured are processed by gravity under heat and pressure through various mixing and distilling vats, filter presses and weighing machines, to emerge in the packing room as the pure compound. Although ventilation is provided and the system is enclosed, fumes and dust particles escape into the atmosphere of the plant and produce the lesions to be described.

The cases reported in this study have, because of potential visual loss and cosmetic blemish, become a matter of concern. I was, therefore, invited to make a survey of the personnel of the plant with the idea of obtaining information relative to the following points: (1) number and types of ocular injuries; (2) manner in which the injuries were incurred and any correlations as to age, duration of employment or other factors producing the lesions; (3) consideration of treatment; (4) estimation of prognosis; (5) prevention of further injury.

NUMBER AND TYPES OF OCULAR INJURIES

Arbitrary, but workable, standards were set up for grading the severity of the lesions. It early became apparent that there was not necessarily any correlation between the severity, or even the nature, of the corneal and the conjunctival involvement. The lesions fell naturally into two groups: (1) conjunctival staining or precipitation of pigment and (2) corneal staining or precipitation of pigment. With the severest corneal involvement observed designated as ++++ and the severest conjunctival involvement as ++++, all the employees sent in for examination were classified by comparison with these standards. This classification having been completed, the patients were regrouped in accordance with the grading of the severity, extent and activity of the lesions. The original classification was completed in December 1943, with subsequent changes in ratings and transferral within the groups, as indicated in figure 1. A study of this chart demonstrates clearly that the length of employment, and inferentially the duration of exposure, is the most constant factor in determining the degree of injury. While in general it may be said that the severe ocular lesions have developed in persons employed five years or longer, the converse is not necessarily true. We feel that the explanation of this paradox lies not in individual sensitivity to the chemical but, more probably, in fortuitous circumstances, which prevented exposure comparable to the time of employment.

Since all the employees presented in the conjunctiva or the cornea more or less evidence of exposure to the chemical, only representative cases of each type will be described.

CASE 8 (presenting the severest corneal damage).—The patient, first observed in August 1943, had been working with hydroquinone for thirteen years. Six months previously, because of visual difficulties, he had been transferred from the plant. His corrected vision was 20/20 in each eye until 1942, when loss of acuity was first observed. The visual rating at this time was 20/30 in the right eye and 20/40 in the left eye. On examination in 1943 the acuity was as follows: O. D. : 20/70; $+2.50 \bigcirc -5.00$, axis $75 = 20/25$; O. S. : 20/400; $+2.50$, axis $110 = 20/25$.

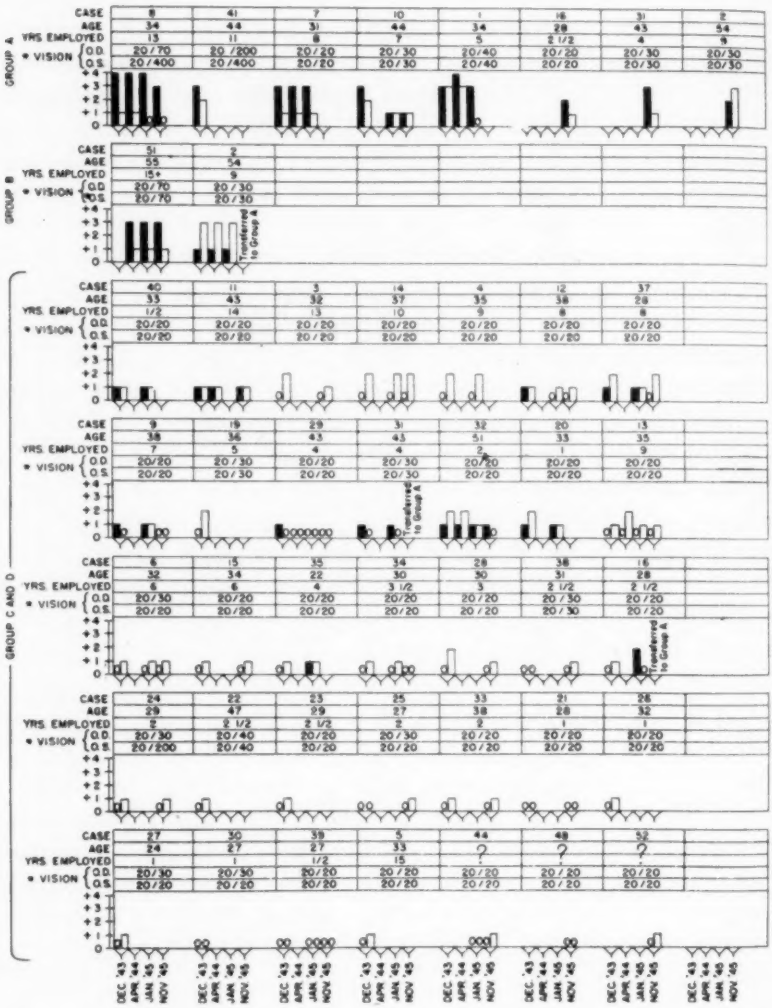


Fig. 1.—Classification of patients with corneal and conjunctival pigmentation engaged in the manufacture of hydroquinone, according to the severity of the lesion and the length of employment.

The asterisks denote corrected vision; black areas, corneal involvement; clear areas, conjunctival involvement, and *O*, no change.

Attention is called to the high cylinders. With the slit lamp, the following features were observed in equal degree in each eye: No gross conjunctival staining was observed near the limbus. Fine, discrete, brownish granules were observed at the limbus in the interpalpebral zone with high magnification. In the superficial layers of the conjunctiva on both the nasal and the temporal side were noted fine, glasslike spherules, somewhat similar to the small inclusion cysts seen in cases of chronic conjunctival irritation but differing in that they seemed to overlie and follow the course of the superficial veins. These cysts also were observed only in the interpalpebral zone. In the superficial layers of the cornea, just under or above Bowman's membrane, were many fine, grayish, translucent and highly refractile dots. These gave an irregular "beaten silver" sheen to the entire cornea. Many fine wrinkles, vertical in distribution, were observed in Descemet's membrane in each eye (fig. 2). The cornea did not stain with fluorescein. There was definite hypesthesia. The terminal corneal nerve filaments appeared slightly larger than usual. The last examination, in November 1945, showed the same

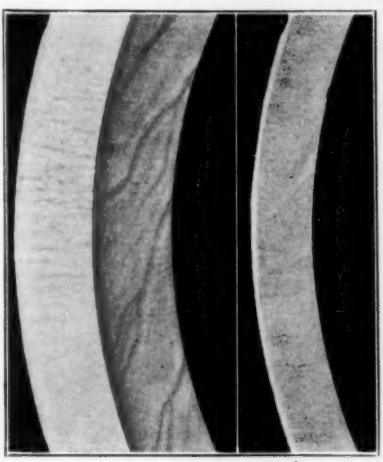


Fig. 2 (case 8).—Severest degree of damage to the cornea in a patient of group A.

corneal picture as that originally described. The refractive error had not changed. There was no photophobia or staining of the conjunctiva. It is assumed that the corneal process is arrested, but the development of keratoconus remains a possibility.

CASE 41.—The patient had worked with hydroquinone for eleven years. Staining had been present for eight years. Visual failure had been observed for four years. The lesions were of identical character in the two eyes. Examination with the low power of the slit lamp revealed a peculiar band-shaped pigmentation of the temporal and nasal portions of the bulbar conjunctiva and of the cornea. This pigmentation was dark greenish brown, most intense on the nasal half of the cornea. The distribution of the lesions in the conjunctiva and the cornea was sharply limited to the exposed interpalpebral zone. On more critical examination with the higher power, two types of pigmentation were noted. First, in the cornea near the limbus, in fact, continuous with the limbus on the temporal side, but with

a small, clear zone approximately 0.5 mm. wide between the limbus and the pigment on the nasal side, were observed many fine, dark brown granules. Similar granules were seen in the conjunctiva. Second, a greenish yellow, homogeneous stain permeated the entire anterior layers of the cornea over the area delineated by the margins of the lids. In the more densely staining area, particularly in the right eye on the nasal side, were several small craters. In these areas it would appear that Bowman's membrane had been invaded. Lying beneath the epithelium, small scarred areas were seen with the narrow beam. These areas of scarring were of various shapes, but were usually a grayish white. They were sometimes confluent and branching. Deeper opacities were seen immediately beneath Bowman's membrane. These were semitransparent and were obviously in the more superficial layers of the stroma. They probably represented edema of these portions of the cornea. The posterior portions of the corneal stroma were clear except that there were numerous vertical wrinkles of Descemet's membrane. The best vision in this case was 20/50 in the right eye and 20/60 in the left eye.

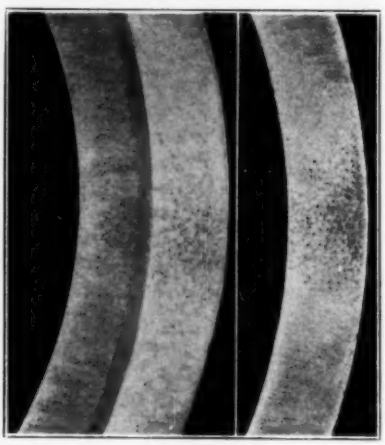


Fig. 3 (case 1).—Severest degree of involvement of the cornea in another patient in group A.

These men (cases 8 and 41), with 3 other persons (cases 7, 10 and 1; fig. 3) were placed in group A. Subsequently, patients 16, 31 and 2 were transferred to this group. All persons in this group showed in approximately equal degree the lesions described in cases 8 and 41. Transferral to group A was considered as making mandatory immediate removal from the plant, a recommendation immediately complied with by the company.

In group B were placed those persons with corneal involvement so severe that the necessity of transfer, working conditions remaining the same, is to be anticipated. Case 2 (fig. 4) illustrates this segment of the total work group.

CASE 2.—The patient showed such progressive involvement in the examination in November 1945 that his transfer was recommended. When he was first seen in January 1944, the conjunctiva in the interpalpebral fissures showed staining. In this area it appeared thickened, almost gelatinous in structure, with embedded brownish green, granular patches standing out in relief. There was no surrounding inflammatory reaction. With the higher power of the slit lamp these granular patches were found to be made up of globules or granules of various sizes, from the barely perceptible to those having a diameter of 1 mm. or more. They varied in color from very dark brown to light yellow. In the periphery of the cornea, with a clear margin intervening, was a belt of superficially deposited, minute

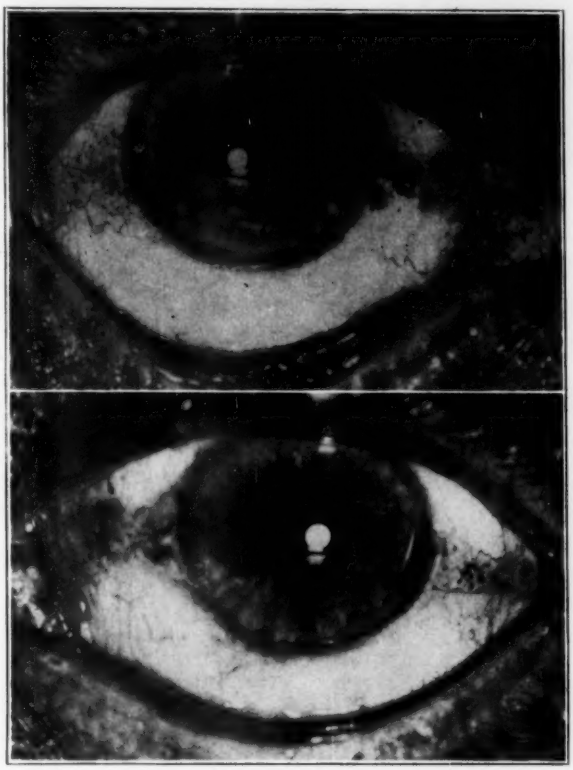


Fig. 4 (case 2).—Appearance of the eyes in a patient of group B, showing corneal involvement.

granules of brownish pigment, resembling except in color the ordinary arcus senilis. It was suggested that possibly this was a fat-soluble material which had become fixed in the fat of the arcus. While the man had no subjective complaints, on account of the degree of staining and the hypesthesia, he was placed in group B, with workers the necessity of whose transfer is anticipated. In November 1945 the absence of inflammatory signs was again noted. The diffuse staining of the conjunctiva was minimal, but the dark brown globules, previously observed to have been plentiful, had apparently increased in size and number. In the inter-

palpebral fissure of the right eye the precipitated pigment extended well over into the cornea in the area usually occupied by an arcus senilis. In addition to the definite granules of pigment in this area, a small area of intense homogeneous pigmentation was observed. In the right eye just below the pupillary area, superficially placed in the stroma of the cornea, was a horizontal white line with one vertical line extending inferiorly on the left side, the scar resembling a reversed and inverted letter *L*. The left eye showed conjunctival pigmentation without corneal changes.

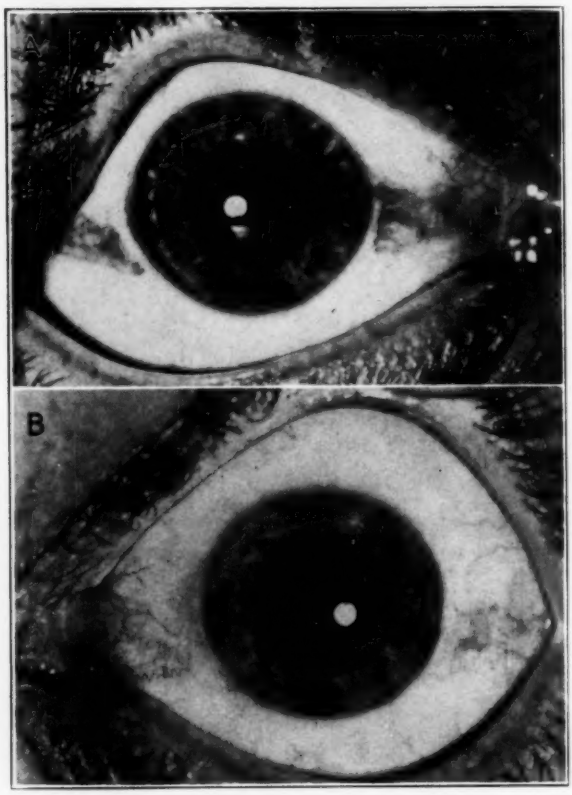
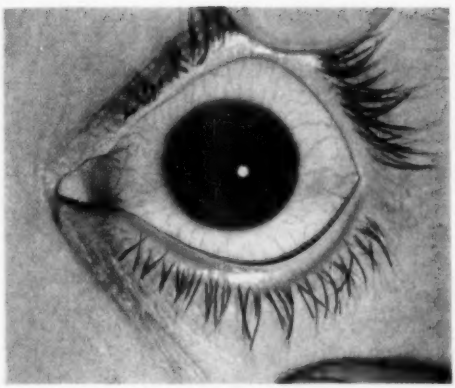
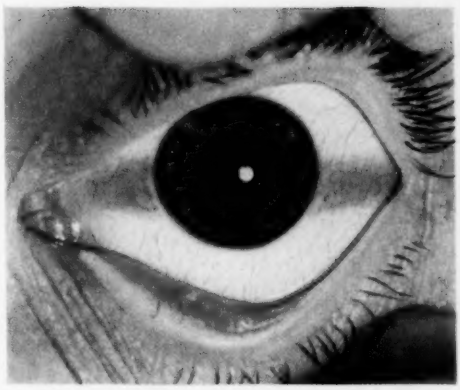


Fig. 5.—*A* (case 14), eye of patient in group C; *B* (case 9), eye of patient in group D.

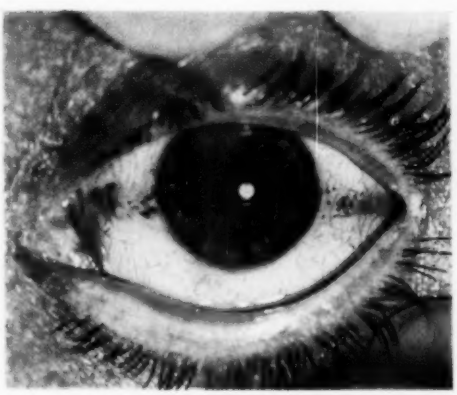
Group C included those men with slight involvement of both the cornea and the conjunctiva, as evidenced by scattered small globules in the conjunctiva with roughening of the corneal epithelium and slight hypesthesia (case 14, fig. 5 *A*). In group D were placed those workers with only barely perceptible involvement, as evidenced by the faint sepia stain, without definite deposition of pigment in the conjunctiva (case 9, fig. 5 *B*). Groups C and D are of interest only in demonstrating



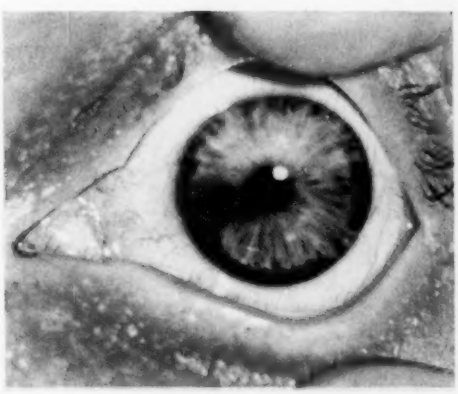
Earliest stage of conjunctival staining. Note horizontal "band" distribution in interpalpebral zone. No corneal stain.



Moderately advanced conjunctival staining. Note diffuse distribution of pigment and clear margin at periphery of cornea.



Advanced conjunctival stain with globular distribution of pigment.



Marked corneal pigmentation. Note relatively slight conjunctival staining.

PLATE 1

how the lesion develops. All workers who had been employed for less than five years, as well as approximately 50 per cent of those employed for longer periods, fell in groups C and D.

One may well speculate at this time on the sequence of events which leads up to the final disability demonstrated by the 8 cases in group A.

MANNER IN WHICH INJURIES ARE INCURRED; SEQUENCE OF DEVELOPMENT OF LESIONS

Development of the lesions as reconstructed from the observations over the two year period would seem to be somewhat as follows:

A man in the early thirties comes into the plant and is trained to work in rotation in any of a half-dozen stations. After a two year interval a brownish tinge against the normally white sclera in the interpalpebral portions is noticeable. When examined with the slit lamp, the conjunctiva in these areas may appear slightly dried and have attached, irregularly and rather firmly to the surface, a white, frothy, foamlike deposit. The deeper portions of the conjunctiva in the same interval assume the light brownish sepia stain. No true microscopic deposition of pigment in definite granules or globules is visible. The cornea remains clear (plate 1, upper left).

After another two or three year interval the conjunctiva appears more thickened and drier, and, in addition to the superficially placed white flecks and sepia stain, small, discrete, dark brown granules or globular precipitates are observed in the deeper structures. Some migration of pigment, from the limbus into the cornea, can now be observed (plate 1, upper right).

After five or more years of exposure a definite increase is noted in the size, number and spread of both the granules and the extent of staining. The cornea has now become gravely involved (plate 1, lower left).

The final stage is seen in case 10 (plate 1, lower right). Vision has become seriously reduced. The patient has been removed from contact with the chemical. The conjunctival staining has cleared, as it apparently does in time. The corneal staining decreases, but permanent damage is done to the cornea, resulting in increased opacity, increase in astigmatism, possibly thinning and keratoconus.

The fifth stage may well be opacity sufficient to necessitate corneal transplantation; the possibility of dyskeratosis, Bowen's disease or epithelioma must be kept in mind.

It will have been observed that in all these cases the chief peculiarity is the limitation of the pigmentation, regardless of its amount and intensity, to that portion of the conjunctiva and cornea within the

interpalpebral fissures. This is the feature which apparently differentiates cases of this condition from others in the scattered case reports of ocular lesions developing after exposure to aniline or its derivatives. That this staining penetrates deeply is proved by a biopsy section of the conjunctiva in case 16 (plate 2), in which the pigment is seen deposited as small granules in the superficial epithelium and as larger granules in the basal epithelial cells. It will be noted that in this section in the proximal portion of the large basal cells are small, finely granular, dark brown deposits, seemingly definitely intracellular. Beneath this, in the subepithelial substance, is a larger, globular, lightly staining, homogeneous mass, poorly defined, with no surrounding inflammatory reaction. Scattered diffusely in the subepithelial spaces, and generally without pattern, are smaller aggregations of pigment. The lighter-staining areas may also be filled with tissue partially saturated with the chemical.

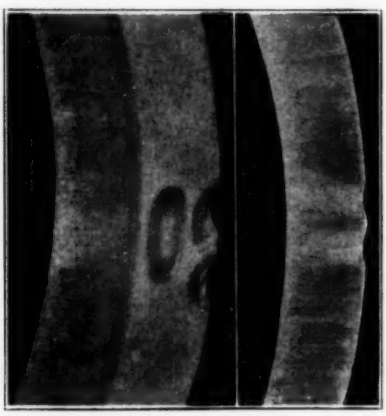
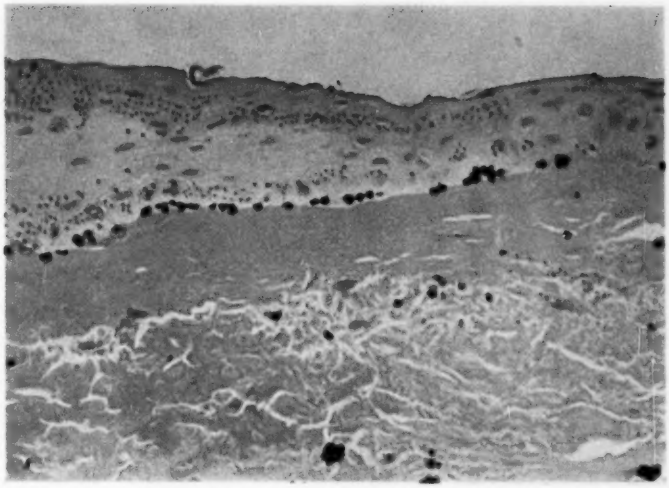


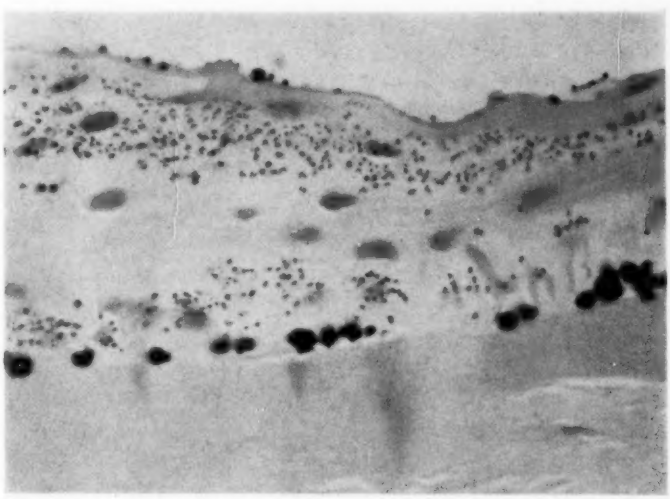
Fig. 6 (case 7).—Abrasion of the superficial epithelium of the cornea by dust particles in a hydroquinone plant.

The question arises as to how the chemical finds its way into these areas and why the staining and precipitation are limited to the exposed interpalpebral portions of the cornea and conjunctiva. Possibly the first break in the defensive barrier is the purely mechanical action of the dust particles striking and abrading the superficial epithelium, as shown in case 7 (fig. 6). According to Cogan's [4] work on corneal permeability, there are in the cornea, and presumably in the conjunctiva, a barrier to water-soluble chemicals in the epithelium and a second barrier to fat-soluble substances in the stroma. Since quinone is both water and fat soluble, these barriers do not afford sufficient

4. Cogan, D. J.; Hirsch, E. O., and Kinsey, V. E.: The Cornea: VI. Permeability Characteristics of the Excised Cornea, Arch. Ophth. **31**:408 (May) 1944.



Photomicrograph from biopsy specimen of conjunctiva; X 300. Note concentration of pigment in basilar epithelial layer.



Photomicrograph from biopsy specimen of conjunctiva; X 1000. Note large globules of pigment in basilar cells proximate to basement membrane and diffuse intracellular distribution of finer pigment granules.

PLATE 2

defense. The pattern of deposition in the proximal portion of the basal cells suggests that these cells have an affinity for the chemical and that until saturated they act as a barrier. I have no explanation for the appearance of the larger subepithelial globules unless it is that the chemical in solution becomes collected, perhaps by surface attraction, into sufficient critical masses in certain intercellular spaces to acquire a different oxidation-reduction potential with relation to this tissue and to become differentiated into these globules. On the basis of such a theory, the relatively undifferentiated sepia-staining tissue might be assumed to be holding the material in unsaturated combination with body fluids.

Since the fat content of the corneal epithelium forms 10 per cent of its dry weight,[5] as compared with 1 per cent of the stroma, the preference of the chemical for this tissue is understandable: Dr. David Cogan, who on one occasion studied these cases with me, in a personal communication draws the following tentative conclusions concerning the previously described lesions:

> The changes seen in the aforedescribed eyes would appear to be of two types: (1) deposition of pigment in the conjunctiva and cornea, and (2) opacification of the superficial portion of the cornea.
>
> The deposit of pigment occurs in the form of spherules of various sizes, is most prominent in the eyes of older patients and is to be observed in regions which normally contain fat, as, for example, in the palpebral portion of the episclera and in the arcus senilis of the cornea. The opacification of the superficial portion of the cornea involves the palpebral fissure only, is most intense in the pupillary area and, while it affects both the older and the younger workers, is the presenting feature of the younger patients who have little deposition of pigment. This opacification is accompanied with folds on the posterior surface of the cornea. This superficial change in the cornea, and not the presence of deposits of pigment, is what causes the eye to be irritable. The inflammatory response varies from photophobia to frank corneal ulceration. The appearance of these superficial changes in the corneas is similar to that induced with formaldehyde vapor, and the clinical course is presumably similar; that is, small erosions recur as a result of the devitalized tissue.
>
> How the pigmented spherules get into subepithelial tissue may be variously judged. It is suggested that the fat-soluble quinone is absorbed through the epithelium, where it is reduced partially, and, becoming less fat soluble, comes out of solution. It would be interesting if those crystals which are frequently seen overlying the spherules are the crystalline form of this product. In any case, the presence of these pigmented spherules apparently is nontoxic, and there is no evidence of their removal by the blood stream, since they do not accumulate around the blood vessels.

5. Krause, A. C.: Biochemistry of the Eye, Baltimore, Johns Hopkins Press, 1934.

Hydroquinone is said to oxidize rapidly to paraquinone, a reaction which may be occurring in the air of the plant at all times. The oxidation is said to be accelerated in an alkaline medium and under certain conditions of moisture and heat. Velhagen [3] observed that if he placed a crystal of hydroquinone on filter paper previously saturated with the alkaline tears, a brownish stain developed very rapidly. He thus reasoned that small crystals of hydroquinone came in contact with the cornea and were there changed to paraquinone, which has the dark brown color. He also assumed that the lowering of the threshold for pain, which in itself is due to the chemical, permits, in turn, a greater exposure to this harmful agent without discomfort, thus setting up a vicious circle. The corneal sensitivity was tested in the 40 men whom my associates and I examined, and we concur in the observation that the loss of sensation is proportional to the degree of staining of the cornea.

Two of our patients (cases 8 and 41) have been hospitalized and subjected to exhaustive tests. Urinalysis and studies of the blood have been performed repeatedly on all persons employed in the plant. No suggestion of systemic intoxication with the drug, which after all is relatively harmless, has been observed. As a matter of record, 12 Gm. was ingested in 1 instance, without fatality.[6] In this case the urine gave a positive reaction for phenol for only three days after absorption of the drug, so that a positive reaction for phenol in our cases, with what must have been minimal absorption, was hardly to be expected. It is the consensus that the absorption is purely local, probably an interaction with the tissues of a chemical which is both water and fat soluble, in an alkaline medium (tears), aided by the mechanical action of the blinking lids.

Assuming that the mechanism of the deposition of the pigment is explained, at least in part, by its affinity for these tissues with a high fat content, one still has to explain the limitation of the staining and precipitation of pigment to the interpalpebral zone. The appearance of the cornea with the slit lamp in the 4 patients with ochronosis described by Smith [7] more closely parallels that of the cornea and conjunctiva in the cases under discussion than any other phenomenon described in the literature. The ocular picture is described as consisting of deposition within the interpalpebral fissures of a band of brownish pigment, extending from the temporal portion of the conjunctiva across the cornea and into the nasal conjunctiva. Fine, brownish yellow spots are seen posterior to the vessels in the conjunctival limbus in the sub-

6. Remond, A., and Colombies, H.: Intoxication par l'hydroquinone, Ann. de méd. lég. **7**:79, 1927.

7. Smith, J. W.: Ochronosis of the Sclera and Cornea Complicating Alkaptonuria, J. A. M. A. **120**:1282 (Dec. 19) 1942.

stance of the cornea. These brownish granules in the cornea are seen in a zone near the limbus and in 1 case were so numerous as to be visible without magnification. These pigment particles are described as "some of pinehead size and others as small as powdergrains." They are located in the more superficial layers of the cornea, probably just below Bowman's membrane, some appearing like droplets; a double convex reflection may be seen, suggesting that some of the pigment spots have a different refractive index; some lie deep, but most of the pigmented areas are in the superficial layers of the cornea.

It has been said that in cases of ocular ochronosis the alkaptonuric patient cannot effect the complete catabolism of the tyrosine and phenylalanine contained in the proteins of the food and tissues, so that an intermediate product, homogentisic acid (2,5-dihydroxyphenylacetic acid, or hydroquinone-acetic acid), remains. Homogentisic acid shares with similar aromatic compounds the property of blackening on oxidation, which explains the dark color of the urine. Pick [8] suggested that in ochronosis through the oxidative ferment tyrosinase the phenol substances in the exogenous group and the homogentisic acid molecule in the endogenous group are changed into melanin pigments which are deposited in the tissues. This is in accord with the belief expressed by Abderhalden and Guggenheim [9] that an accumulation in the human organism of excessive and abnormal amounts of substances possessing the oxyphenol groups leads to the production of melanin pigments by action of ferments.

We assume, then, that the chemical hydroquinone, or some modification thereof, goes into solution in an alkaline aqueous medium (tears). Since the substance is fat soluble, it is also combined in the cornea and conjunctiva by some interaction with fat in the normal reservoirs and with the fat present as a result of insult and injury to the cornea. This "bound" material in the interpalpebral fissure, being exposed both to light and to the specific effect of the intracellular oxidase, which acts in the presence of radiant energy, undergoes modification in structure similar to the intermediate products of hydrocarbon metabolism in ochronosis, producing a melanin-like material deposited in these fat reservoirs.

This assumption, it must be admitted, has no experimental backing. Attempts to reproduce the pigmentation were unsuccessful in rabbits, in that exposure to fumes and solutions of such strength as not to produce

8. Pick, L.: Ueber die Ochronose, Berl. klin. Wchnschr. **43**:478, 1906.

9. Abderhalden, E., and Guggenheim, M.: Versuche über die Wirkung der Tyrosinase aus Russăla delica auf Tyrosin, tyrosinhaltige Polypeptide und einige andere Verbindungen unter verschiedenen Bedingungen, Ztschr. f. physiol. Chem. **54**:331, 1908.

more specific inflammatory reaction would not produce the lesion, possibly because the albino rabbit does not carry in its cell the oxidizing enzyme which is capable of reacting on this substance.

TREATMENT

The problem of treatment may be disposed of by the mere statement that there is no really effective therapy other than prevention. Possibly some of these patients may later be candidates for contact lenses or keratoplasty.

PROGNOSIS

The prognosis in our cases may be further judged by the statement of Lewin and Guillery,[10] that the cause of corneal lesions in workers engaged in certain dyeing procedures is the presence of quinones in the vapors. These authors stated that these quinones precipitate on the cornea and conjunctiva and cause injury by contamination of these areas by the worker's rubbing the affected parts with the fingers and hands. This corrosive effect on the cornea is paralleled by pigmentation of the cornea. By continued repetition of this injury, the epithelium of the cornea may be completely undermined, and penetrating sepia brown pigmentation and turbidity of the parenchyma, a serious reduction of the visual acuity and symptoms of severe keratoconjunctivitis may be produced. In some instances distinct vesicular ulcers of the cornea may result. According to Lewin and Guillery, involvement of the cornea improves on discontinuation of the exposure and with ordinary treatment, such as that used for keratitis, within several months to one year. The epithelium regenerates; the pigmentation decreases, and the visual acuity is improved.

I do not believe that the facts justify any such sanguine attitude toward the ultimate outcome in the cases we have described. Keratoconus and ulceration are possible complications. Patient 8 shows some evidence of keratoconus, and in Velhagen's [3] second case there was a history of ulceration. With the slit lamp we noted enlargement of the terminal nerve filaments in several cases. The deleterious effects of phenol, dinitrophenol and other such chemicals on the peripheral nerve mechanism are well known, and it is probable that, as a result of these changes, trophic disturbances, which are notoriously resistant to the reparative measures of the body, may have developed in the cornea. Prolonged exposure has produced corneal dystrophy, dyskeratosis and perhaps keratoconus. While the drug is of minimal toxicity and does not belong to the carcinogenic group, some of the lesions we have seen resemble

10. Lewin, L., and Guillery, H.: Die Wirkungen von Arzneimitteln und Giften auf das Auge, in Handbuch für die gesamte ärztlichen Praxis, Berlin, A. Hirschwald, vol. 1, p. 728; cited in letter from chief industrial toxicologist, United States Public Health Service.

clinically Bowen's disease. The possibility of the later development of a frank malignant growth in some cases must be kept in mind.

PREVENTION

The question of prevention of further injury becomes a matter of improved housekeeping, better ventilation, personal hygiene and, possibly, the use of goggles. Further injury in specific cases is being avoided by removal from the vicinity of the plant of those persons whose corneas show early staining. In this connection, it is well to note that once the cornea is extensively damaged and the terminal nerve filaments are injured, the disappearance of the stain does not necessarily connote improvement. Case 8 is an example of this corneal damage, which persists or increases after the stain has disappeared. In all cases the lesions have been slow to develop, and routine examination with the slit lamp should determine when tolerance has been reached.

SUMMARY AND CONCLUSIONS

Observations are presented on a group of workers employed in the manufacture of quinone and hydroquinone in whom certain characteristic lesions of the cornea and conjunctiva have developed.

These lesions consist of (1) a variable degree of pigmentation of the interpalpebral portions of the conjunctiva and cornea, proportional to length of employment and to age, and (2) corneal changes, which may be due in part to the corrosive action of the chemical, but which, in view of its obvious failure to stimulate inflammatory reaction in the conjunctiva, are more probably the result of migration or penetration of the chemical into the corneal structure, in the same manner as the invasion of the conjunctiva occurs, with a variation in response due to the peculiarities of the corneal structure. These changes consist in pitting and erosion of the corneal surface, thinning of the cornea, development of irregular pigmented or staining areas (which may or may not simulate Stähli's lines), wrinkling or modification of Descemet's membrane and, possibly, keratoconus. The changes are apparently reversible up to a certain point in that conjunctival staining may disappear. The corneal stain is more permanent.

Since only those portions of the conjunctiva and cornea in the interpalpebral space take the stain, it is assumed that some reaction takes place between chemical and tissue which is possible because of a peculiarity in structure limited to this area, or of the additional effect of light on the chemical and tissue. The possibility is suggested that this change in the limited area may be somewhat analogous to the deposition of pigment in the interpalpebral fissures associated with ochronosis.

Since the lesion could not be produced in rabbits, it must be assumed that in man some additional, and as yet unknown, factor must exist, or that the rabbits, being albinos, did not possess the specific intracellular oxidase necessary to the formation of this melanin-like substance. The chemical is relatively harmless so far as its immediate effects can be determined.

Prolonged exposure has produced corneal dystrophy and dyskeratosis, and perhaps, keratoconus. While the chemical is said not to belong to the carcinogenic group, some of the lesions resemble Bowen's disease. The development of a frank malignant growth is not beyond the bounds of probability.

Clinical Notes

BETA RAY RADIUM APPLICATOR FOR OCULAR USE

Preliminary Report

CHARLES E. ILIFF, M.D.
BALTIMORE

THE VALUE of beta irradiation in the treatment of certain ocular lesions is well recognized, but the difficulty in obtaining the radon for the Burnam applicator has greatly limited its use. Accordingly, a beta ray radium applicator was designed which would as nearly approach as possible the performance of the Burnam applicator. In order to understand the use of this radium applicator, the differences between radon and radium must be appreciated and the construction of the applicator understood.

Radon is a gas, a breakdown product of radium, and one hundred thousand times as active, weight for weight, as the radium in the form of salt. It is thus possible to concentrate in a very small space an extremely high potential of radioactivity. The breakdown rate of the radon is extremely rapid, as the half transformation time is 3.83 days. In the Burnam applicator a radon seed of 5 mm. diameter, containing 200 to 500 millicuries of radon, is used. Beta and gamma rays are emitted from the radon as from an apparent point source at the center of the seed. The seed is placed in a brass cylinder with walls 2 mm. thick and with an open window, 4 mm. in diameter, at one end. Through this window beta rays pass unfiltered. The gamma rays pass out from the seed in all directions, as they are only slightly filtered by the brass cylinder.

THE APPLICATOR

In the construction of the radium applicator here reported, the plaque form was found to be the most satisfactory. The plaque is really a small portable radon plant, the radon being given off from the radium salt contained therein. The radium must be spread in a layer so thin that it does not in itself act as an appreciable filter of the beta rays, and thus it is not impossible to use more than 50 mg. in an ocular applicator of convenient size. The radon is held in the interstices of the radium salt, and the beta rays are given off as a surface fire, rather than as the point source fire emitted from a radon bulb. For this reason, any radium ocular applicator would deliver per unit area only one-quarter to one-fifth the amount of beta radiation delivered by a radon bulb of equivalent strength. This extremely important point limits the use of the plaque applicator to those conditions which can be treated with surface fire.

From the Wilmer Ophthalmologic Institute of the Johns Hopkins Hospital and University.

The beta rays from the radium applicator are filtered both oy the radium salt and by the 0.1 mm. "monel" metal face plate, so that the delivered output is 30 milliequivalents. This must be contrasted with the 200 to 500 millicurie content of the Burnam radon applicator.

The half-transformation time of radium is over fifteen hundred years; so deterioration is not an important factor.

In summary, in the radon applicator, there is a point source of radiant energy ranging from 200 to 500 millicuries, with a very short half-transformation time. The radium applicator, on the other hand, has a low potential, a wide surface fire, rather than a point fire, and what might be termed an unlimited life expectancy.

In a previous communication [1] the use of the Burnam applicator was discussed in detail in the treatment of vernal conjunctivitis, tuberculous scleritis and small tumors of the anterior ocular segment and in the occlusion of vessels and the prevention of fibrous overgrowth. In the treatment of vernal conjunctivitis, tuberculous scleritis and tumors of the anterior segment, the fact that the radium applicator delivers a surface fire rather than a point source fire is not a disadvantage. However, it is not practical to treat a lesion the size of an individual vessel or a number of small vessels with surface fire, since the object of such treatment is to occlude the vessel itself by producing endarteritis, with as little damage as possible to the surrounding tissues. For this, the point source fire of the radon applicator is ideal, and the wide surface fire is not satisfactory.

A kidney-shaped applicator with a foot plate of concave scleral curvature was considered, but the technical difficulties in production of such an applicator overbalanced its possible advantages. Therefore, a rectangular applicator measuring 6 by 12 by 6 mm. and containing 50 mg. of radium salt was made. The sides and back are of silver and measure 1.0 and 3.0 mm., respectively, and the face plate is 0.1 mm. of "monel" metal. A handle 28 cm. in length is screwed into the back of the plaque (fig. 1). A ten minute treatment time is required to give a delivered contact dose of 4 gram seconds per unit area. A holder for the applicator is, therefore, important. The holder pictured in figure 2 consists of four brass bars with swivel joints, which can be moved in any direction to permit the application at the desired angle.

The ten minute application time in the treatment of lesions of the lid is associated with no particular discomfort or inconvenience. A lid speculum is necessary in the treatment of scleral lesions, and application of tetracaine ointment five minutes before the treatment greatly reduces the discomfort. The patient is placed in the treatment chair next a screen or wall, on which a mark can be made for the fixation of the eyes in the desired position. A time clock, such as that used by photographers, was found to be quite satisfactory. Ten minute applications, delivering doses of 4 gram seconds, can be repeated after an interval of one week, and again the second week, the total dose remaining well below the contact skin erythema dose of 18 gram seconds. Such a course of therapy could be repeated after an observation period of two to three

1. Iliff, C. E.: Beta Irradiation in Ophthalmology, Arch. Ophth. **38**:415 (Oct.) 1947.

weeks and at intervals as found necessary for the patient's improvement. In treatment of lesions smaller than the face plate of the applicator, 0.5 mm. of sheet lead is found useful as protection to the surrounding tissue. The lead can be cut with scissors to any desired shape and

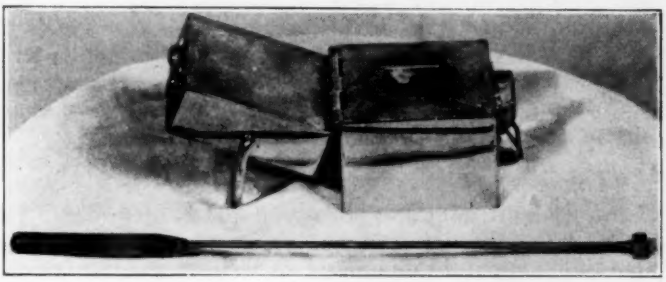


Fig. 1.—Radium applicator, with lead carrying case, manufactured by the Radium Chemical Company, Inc., New York.

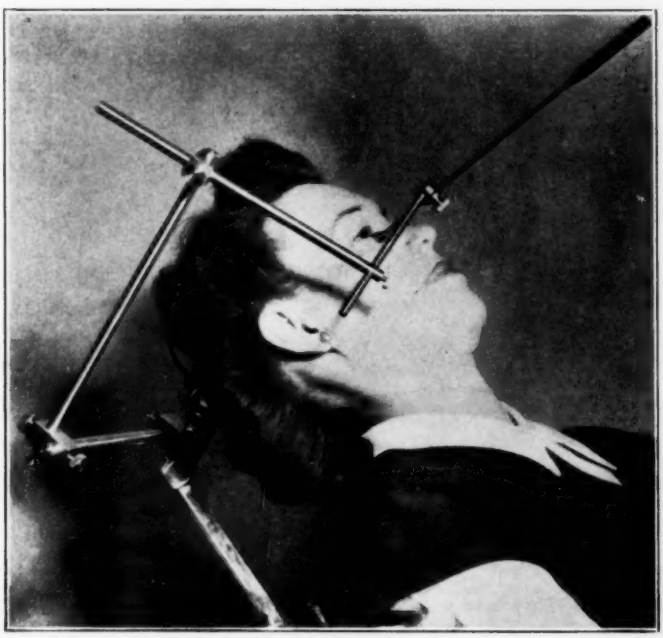


Fig. 2.—Holder for radium applicator, made by Mr. Albert Goebel, Wilmer Ophthalmological Institute. The applicator is shown in contact with the papilloma of the lid.

molded easily to fit the lesion. In some cases of papilloma or tumors of the lid, a cross fire technic and a total treatment time as high as thirty minutes at one period were employed.

SAFETY FACTORS

The 28 cm. handle on the plaque provides an adequate factor of safety for the operator. It is unwise for the physician to hold the lid during treatment or to handle the plaque itself. All the usual precautions for radium and roentgen therapy should be observed. The relation of outputs of beta and gamma rays in the radium applicator differs slightly from that in the radon applicator. However, the proportion of gamma rays is still well within the range of safety, and there is no danger of cataract formation if the operator observes the general rules for beta ray therapy presented in the previous communication.[1]

SUMMARY

A beta ray radium applicator for ocular use is presented. The time of application is greatly increased, and its use as compared with that of the Burnam radon applicator is limited. Owing to the low potential and the surface fire, the use of the radium applicator is limited to treatment of vernal conjunctivitis, tuberculous sclerokeratitis and small tumors of the anterior segment and to the prevention of overgrowth of fibrous tissue. It is not useful in the occlusion of vessels. The instrument should be applied by means of a holder of some form. The usual precautions in using all radiation therapy should be observed. It is felt that the radium applicator, although it cannot duplicate the performance of the radon applicator, will fill a definite need as an addition to the instruments that are available to the ophthalmologist in the treatment of the aforementioned lesions.

12 West Read Street (1).

OINTMENT ABSORBED THROUGH CORNEAL WOUND

Report of a Case

DONALD K. BINDER, M.D.
SCHENECTADY, N. Y.

That the instillation of ointment into the eye after a penetrating wound is not without danger is illustrated by the case reported here.

REPORT OF CASE

C. P., aged 43, a machine operator was struck in the right eye with an unknown object while at work. He was treated at the first aid station of his employer, where an ointment was instilled, the nature of which is not precisely known but which is believed to have been a sulfonamide preparation.

He was seen by me shortly thereafter, when I found that he had a small perforating linear wound just below the center of the cornea. The anterior chamber was formed, but there was injury to the lens with partial traumatic cataract. Within the anterior chamber there were two spherical yellowish globules, each approximately 1 mm. in diameter—one situated in the upper part of the limbus and the other in the limbal region at 9 o'clock. The nature of these foreign bodies was obscure. The patient was hospitalized, and roentgenographic study failed to reveal an intraocular foreign body. He made a good recovery, and the eye became white. However, the two globules coalesced, to form one. The globule was

apparently lighter than the aqueous fluid, as it always sought the highest point in the anterior chamber, much as does the air bubble in a spirit level. If the patient stood up the globule would move to the upper part of the limbus (figure 1 [1]); if he lay down on one side it would move to the opposite angle of the chamber, and if he was supine it would move to the center of the anterior chamber and interfere with his vision.

A colleague who had occasion to see the patient [2] suggested that the foreign material might be ointment. He informed me that he had had a case in which ointment had entered the eye but eventually had disappeared. I therefore waited approximately six months to see whether this would happen.

I was also informed by the medical department of a leading pharmaceutical house that if ointment did enter the eye it would not be likely to form a globule but, rather, would produce a diffuse haziness, since the usual ointment base has a melting point which is below the temperature of the aqueous fluid.[3]

Position of the globule in the anterior chamber when the patient was standing.

Through a keratome incision at the upper part of the limbus the foreign material was evacuated, and in the process its gelatinous nature was revealed Unfortunately, the amount which could be saved was not sufficient for examination. A good recovery was made.

It is interesting to note that after the operation macular changes developed in the other eye, which reduced vision from 20/20 to 20/50, with no other pathologic alterations.

The almost routine use of ointment after intraocular operations by many surgeons and in many institutions with no report of any penetration into the anterior chamber would indicate that the possibility of this complication exists principally when there is a direct corneal wound. The mechanism of penetration, I presume, is some phenomenon of aspiration. A search of the literature of the past twenty years revealed that only 1 such case had been reported.[4] A foreign body deeply

1. Dr. E. Kellert, Ellis Hospital, Schenectady, N. Y., made the photograph.
2. Personal communication to the author.
3. Abbott Laboratories: Personal communication to the author.
4. Tetze, H. M.: Unusual Retrocorneal Phenomenon (Globule of Prontosil in Anterior Chamber), Brit. M. J. **1**:665 (May 29) 1943.

embedded in the cornea was removed, with perforation and escape of the aqueous fluid. An ointment containing azosulfamide (disodium 4-sulfamidophenyl-2'-7'-acetylamino-1'-hydroxynaphthalene-3',6'-disulfonate) was instilled and entered the anterior chamber, where it remained. It was concluded that the entrance was due to the pressure of the bandage.[4]

SUMMARY AND CONCLUSION

A case is presented illustrating the entrance of ointment into the anterior chamber following a penetrating wound of the cornea. This ointment was not absorbed and necessitated removal.

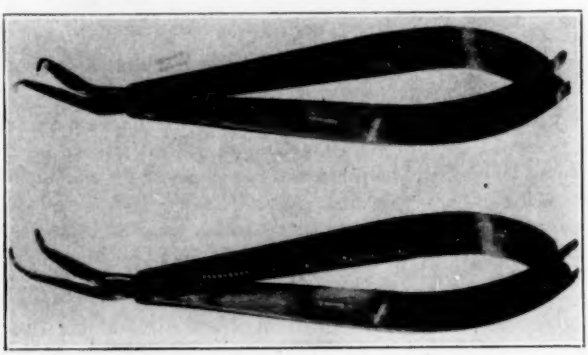
After perforating wounds of the cornea one should not use ointment in the eye.

102 Barrett Street (5).

IMPROVED SCISSORS FOR CORNEAL GRAFTING

HERBERT M. KATZIN, M.D.
NEW YORK

The choice of round versus square corneal grafts for use in partial penetrating keratoplasty has been resolved by some authors in favor of the square type because of the facility of excision of the square graft with the straight-bladed scissors. I felt, however, that the ease of outlining a round graft and its superior cosmetic properties were worth consideration and devised a pair of scissors which were curved to the



Scissors for corneal grafting curved to the diameter of the round graft.

diameter of the round graft. These scissors made the completion of the trephine incision much easier than it had been heretofore. The most recent model of these scissors is fashioned after Castroviejo's straight keratoplasty scissors. They are made up of right-handed and left-handed curves, so that the operator need not move his position from the

From the Corneal Research Laboratory, under the auspices of the Ayer Foundation.

head of the table, and in a 5, 6 or 7 mm. diameter curve, depending on the size of the trephine used. They have been employed in many transplantations, both experimental and clinical, with entire satisfaction.

These scissors make it possible to perform the entire corneal section without danger of injury to the lens. The anterior chamber may be entered with a Wheeler knife, instead of trephining through the cornea, in cases in which the eye is soft, the chamber shallow or the cornea so opaque that the structures of the anterior segment cannot be seen.

1148 Fifth Avenue.

Abstracts from Current Literature

EDITED BY DR. WILLIAM ZENTMAYER

Anatomy and Embryology

SURGICAL ANATOMY OF THE FACIAL NERVE: WITH REFERENCE TO THE TECHNIQUE OF ORBICULARIS BLOCK (PALPEBRAL AKINESIA). M. KLEIN, Brit. J. Ophth. **30:** 668 (Nov.) 1946.

Review of the literature on facial akinesia shows three approaches: the terminal branches, the main trunk at the stylomastoid foramen and the middle portion of the course of the nerve near the ramus of the mandible. Dissections have shown that the surface marking of the middle portion of the facial nerve corresponds to a horizontal line drawn through the junction of the upper and the middle third of the distance between the zygoma and the angle of the mandible. The position of the nerve within the parotid gland is in a plane of cleavage between the two lobes of the gland, which may facilitate the spreading of the procaine into the nerve. The correct point for the injection, when the middle portion of the course of the facial nerve is used for palpebral akinesia, lies below the condyloid process, at the junction of the upper and the middle third of the distance between the zygomatic arch and the angle of the mandible.

W. ZENTMAYER.

Conjunctiva

PEMPHIGUS CONJUNCTIVAE. F. W. NEWELL and J. S. GREETHAM, Am. J. Ophth. **29:** 1426 (Nov.) 1946.

Newell and Greetham define, describe and briefly review the literature of pemphigus. They report 3 cases, 1 of which was complicated by bilateral uveitis with complicated cataract.

W. S. REESE.

THE CYTOLOGY OF CONJUNCTIVAL EXUDATES. P. THYGESON, Am. J. Ophth. **29:** 1499 (Dec.) 1946.

Thygeson studied smears and conjunctival scrapings in 2,000 cases of conjunctivitis of diverse causes. He found that variations in leukocytic reactions and epithelial changes were sufficiently great to have diagnostic value, and he recommends that a statement on the cytologic character be a part of every laboratory report on conjunctival scrapings or exudates.

W. S. REESE.

SEED GRAFTING OF THE CONJUNCTIVA IN THE TREATMENT OF SYMBLEPHARON. A. HAGEDOORN, Am. J. Ophth. **29:** 1568 (Dec.) 1946.

Hagedoorn describes a case of total symblepharon of the inferior eyelid treated by means of small "seed" grafts from the conjunctiva of the same eye, in combination with a (Stent's) mold. Light perception

and accurate projection were obtained. A colored contact glass was inserted. Both subjective and objective results were good.

W. S. REESE.

Congenital Anomalies

BILATERAL PARTIAL COLOBOMA OF THE OPTIC NERVE. J. A. MAGNUS, Brit. J. Ophth. **30:** 692 (Nov.) 1946.

The right eye showed a disk at least twice the normal size, deeply cupped below and to the nasal side. The upper branches of the central retinal vessels emerged a little above the center of the disk, whereas the lower branches emerged at the circumference of the disk and bent sharply around the edges. The disk in the left eye was of equal size with the disk in the right eye. The upper branches of the retinal vessels entered by the central part of the disk, whereas the other retinal vessels entered along the lower edge of the disk. Some of them were branches of the short ciliary arteries. There was slight cupping below and to the nasal side. The visual field of each eye showed a deep depression above, caused by a nerve fiber bundle scotoma, whereas the lower half of the field was normal. These field defects corresponded to the deeply cupped parts of the disk.

W. ZENTMAYER.

Experimental Pathology

CHEMICAL BURNS OF THE RABBIT CORNEA. C. P. CARPENTER and H. F. SMYTH JR., Am. J. Ophth. **29:** 1363 (Nov.) 1946.

Carpenter and Smyth found from experiments on rabbits that alkaline molecules become bound to the epithelial cells of the cornea and are not removed by prolonged washing, but that the alkali is slowly liberated, thus resulting in a progressive burn. Attempts to neutralize this alkali were not successful, and denudation of the cornea failed to demonstrate its effectiveness, owing apparently to species differences in the rate of epithelial regeneration.

W. S. REESE.

General

DEPOSITION OF MERCURY IN THE EYE. I. ABRAMOWICZ, Brit. J. Ophth. **30:** 696 (Nov.) 1946.

A woman aged 57 had used an ointment containing ammoniated mercury on the lids continuously since she was 16 years old for the relief and prevention of blepharitis. For the past ten years the skin of the lids had been bluish gray, and the conjunctiva was hyperemic. Biomicroscopic examination showed dark pigment granules in the bulbar conjunctiva, especially near the cornea, with preferential distribution around the perivascular spaces. In the periphery of the cornea in the region of Descemet's membrane occurred a discoloration, varying from greenish gray to bluish gray. A yellowish brown, lusterless opacity occupied the pupillary area of the lens just under the capsule.

W. ZENTMAYER.

STRANGE OCULAR COMPLICATION CAUSED BY SULFADIAZINE POISONING. D. PRADO, Arq. brasil. de oftal. **8:** 169 (Dec.) 1945.

A man aged 24 was first examined in November 1944. The ocular condition had started in June of that year, after prolonged treatment with sulfadiazine. The initial ocular symptoms were severe conjunctival irritation, a sensation as of sand in the eye, slight photophobia and lacrimation, high fever, headache and a generalized rash. After three days the eyelids were closed by a conjunctival exudation. About five months later there were narrowing of the palpebral fissures, marked trichiasis, lacrimation and small subconjunctival hemorrhages in both eyes. The corneas were normal. An unusual finding was the presence of a symmetric symblepharon, with vertical bands in the internal and the external angle of both eyes. Depilation with the diathermic current was performed, with relief of the condition. The aspect of the conjunctivas, however, remained the same.

M. E. ALVARO.

General Diseases

OCULAR MANIFESTATIONS OF AVITAMINOSIS. R. DE TOLEDO, Arq. brasil. de oftal. **8:** 173 (Dec.) 1945.

The author reviews the several ocular disturbances caused by avitaminosis. Xerosis and keratomalacia are due to lack of vitamin A. These ocular symptoms are characterized by loss of brilliance of the cornea and the presence of Bitot spots. They are not early symptoms, however, and are usually associated with other signs, such as night blindness and disturbances of the skin and glands. Experimental cataract in rats due to vitamin A deficiency has been observed. Blepharokeratoconjunctivitis, especially in children, has been known to respond promptly to treatment with vitamin A in numerous cases. Night blindness is also a well known sign of vitamin A deficiency. The most frequently observed avitaminoses of the B group are the superficial keratitides. Deficiencies due to the vitamin B complex seem to affect the optic nerve more severely than the other ocular tissues. Thiamine deficiency causes a noninflammatory neuritis without degeneration of the nerve fibers. Retrobulbar neuritis is also associated with deficiency of the vitamin B complex. Besides the oculomotor disturbances, such as isolated paralysis and paresis of certain extrinsic muscles. Wernicke's syndrome (superior hemorrhagic polioencephalitis) has also been attributed to a lack of thiamine. Ascorbic acid is useful in the medical treatment of cataract. Vitamin D is successfully used in cases of blepharitis, conjunctivitis, keratoconjunctivitis and myopia. Vitamin K preparations have been widely used in cases of ocular hemorrhages, and the tocopherols (vitamin E) have been stated to be useful in the treatment of parenchymatous keratitis and keratoconus.

M. E. ALVARO.

Glaucoma

GLAUCOMA CAPSULARE. H. S. GRADLE and H. S. SUGAR, Am. J. Ophth. **30:** 12 (Jan.) 1947.

Gradle and Sugar give a brief history of glaucoma capsulare, describe its zones of capsular exfoliation and differentiate it from simple glau-

coma. They cite several cases to illustrate its clinical aspects and state that removal of the lens has no great effect on the ocular hypertension.

W. S. REESE.

INFLAMMATORY JUGULAR PHLEBOSTENOSIS AS THE CAUSE OF GLAUCOMA EXOGENICUM. O. MEYER, Brit. J. Ophth. **30:** 682 (Nov.) 1946.

Glaucoma exogenicum has its cause outside of the eye in cases of chronic proliferative endophlebitis of the jugular veins. Jugular endophlebitis has a narrowing effect on the lumen of the vein, which interferes with venous drainage of the head region. Blockage of the proximal portion of the jugular vein produces an increase in venous pressure in all distal veins, including the episcleral veins, which drain the veins of Schlemm's canal. The deciding factor in a normal drainage of the aqueous humor from the anterior chamber is the difference between the higher pressure in the anterior chamber and the lower pressure in the veins of Schlemm's canal and the episcleral veins. If the venous pressure of the veins in Schlemm's canal and the episcleral veins equals or exceeds the intraocular pressure, the slope in pressure is eliminated and the drainage of the anterior chamber is stopped completely. The treatment of exogenic glaucoma resolves itself into a recalibration of the jugular veins.

W. ZENTMAYER.

Hygiene, Sociology, Education and History

SOME HISTORICAL NOTES ON SPECTACLES AND ON BERYLLUS. G. TEN DOESSCHATE, Brit. J. Ophth. **30:** 660 (Nov.) 1946.

It is generally held that Roger Bacon (1214-1294) was the first European scholar to mention the practical utility of lenses. He, however, was anticipated by Robert Grosseteste (1175 ?-1253), who, so far as the author knows, was the first scholar in Western Europe to write on optics. A third Englishman, John Peckham (1228-1294), is renowned for his work "Perspectiva communis."

Beryl is the name applied to the precious stone, including the emerald, the aquamarine and other transparent varieties known as "precious beryl," with certain coarse opaque varieties unfit for use as gems. In Meyer's "Konversations-Lexicon," it is stated that the German word *Brille* is derived from *Berilli,* the name of "transparent pieces of stone and glass." Curative powers were ascribed to *beryllus.* It seems possible that when men first used spectacles they believed that improvement of visual acuity was caused by the pharmacologic power of the gem.

W. ZENTMAYER.

Injuries

CHEMICAL BURNS OF THE HUMAN CORNEA. R. S. MCLAUGHLIN, Am. J. Ophth. **29:** 1355 (Nov.) 1946.

From a study of 500 cases, McLaughlin concludes that with chemical burns of the cornea immediate first aid followed by long flushing with water is of utmost importance and that denudation of the cornea is the treatment of choice.

W. S. REESE.

BLUE HALOES IN ATABRIN [QUINACRINE] WORKERS. I. MANN, Brit. J. Ophth. **31:** 40 (Jan.) 1947.

The present note concerns the ocular condition of 6 workers engaged in the production of quinacrine (atabrine) and its compression into tablets. Despite the wearing of protective clothing, goggles and masks, the dust was so fine that the workers soon noticed yellow staining of the conjunctivas and skin, especially of the hands, head and neck. After several weeks or months each one noticed that when looking at a small point of light he saw a blue halo around it. Visual acuity was found to be 6/6 in all eyes. In connection with the yellow discoloration in the interpalpebral space, there was a curious slight dulling and yellowing of the cornea. Examination with the slit lamp showed aggregations of minute dark brown dots at the limbus in the exposed portion and just under the edge of the lower lid. The whole surface of the cornea was covered with yellowish brown, dustlike particles. The surface was perfectly smooth and bright, so that it seems likely that the particles were situated in the substance of the corneal epithelium. Across the lower part of each cornea was a series of wavy yellow lines composed of aggregated dots. No permanent damage appears to have resulted. It is possible that the particles were precipitates of an insoluble breakdown product of quinacrine. The halo was obviously a diffraction effect, due to the opaque granules in the epithelial cells. The article is well illustrated with colored plates.

W. ZENTMAYER.

Lens

CATARACTA GLAUCOMATOSA ACUTA. H. S. SUGAR, Am. J. Ophth. **29:** 1396 (Nov.) 1946.

Sugar reports 6 cases of acute glaucomatous cataract and summarizes the literature. The condition is important chiefly in differential diagnosis and in establishing the diagnosis of a previous attack of acute glaucoma.

W. S. REESE.

CONTRIBUTIONS TO THE SURGERY OF CONGENITAL CATARACT. W. F. MONCREIFF, Am. J. Ophth. **29:** 1513 (Dec.) 1946.

Moncreiff suggests discission as the method of choice in cases of congenital cataract, followed by irrigation of the anterior chamber with the fluid directed toward the posterior capsule and the center of the pupil. This is designed to remove cortex from the capsular sac and displace it into the anterior chamber. He does not incise the posterior capsule and emphasizes the need of maximal mydriasis. Three cases are reported.

W. S. REESE.

ECTOPIA LENTIS CONGENITA. W. P. C. ZEEMAN, Acta ophth. **20:** 1, 1942.

Of 45 eyes with congenital ectopia lentis which had not received any surgical treatment, retinal detachments were found in 5 and cataract in 8. Glaucoma occurred in 5 eyes. Myopic changes in the fundus accounted for the very poor vision in 3 other eyes.

On 17 eyes operation was performed by various methods. Good results were obtained in 13 eyes. Two eyes retained diminished function (15/60 to 5/60); 2 eyes, less than this. The author stresses the complications that occur with various surgical procedures. Everything considered, he favors discission of the lens with two needles.

O. P. PERKINS.

ELECTRIC CATARACT AND ELECTROCARDIOGRAPHIC CHANGES AFTER SHOCK. E. GODTFREDSEN, Acta ophth. **20:** 69, 1942.

A case is recorded in which electric shock resulted in changes in the lens in the form of capsular vesicles, which gradually disappeared, leaving a permanent subcapsular opacity with reduced vision.

Electrocardiographic studies disclosed changes suggesting a coronary lesion and signs of disturbance in the conduction system. The importance of early ophthalmic and electrocardiographic examinations in cases of electric shock is pointed out, with special reference to possible claims for compensation.

O. P. PERKINS.

Neurology

NYSTAGMUS: AN APPRAISAL AND A CLASSIFICATION. R. N. DEJONG, Arch. Neurol. & Psychiat. **55:** 43 (Jan.) 1946.

DeJong has written an appraisal and classification of the varieties of nystagmus, with an excellent review of the literature, including the important references. He describes nystagmus as to type, form, direction, rate, amplitude, duration and intensity, and as to the relation of the response to movements of the eyes, head and body. He reviews the methods for the delineation and recording of nystagmus.

DeJong states: "Nystagmus must not be regarded as an entity, for there are many types of nystagmus which appear to serve widely diverse purposes. The position of the eyes is influenced reflexly by impulses coming from the retinas, the ocular muscles, the labyrinths and the cochlea and by proprioceptive impulses arising from movements of the head or body. It is also influenced by impulses arising centrally from the motor cortex. Nystagmus may, in most instances, be considered a compensatory reaction of the eyeballs to defective or abnormal impulses arising from any of these sources. It may serve many apparent purposes: namely, . . . to keep the eyes as long as possible in the same position in relation to the visual field; to increase incoming impulses; to aid in ocular fixation, and to assist in orientation in space."

The rapid and the slow component of nystagmus and their significance are discussed; the methods used to induce nystagmus clinically or experimentally, with the interpretation of deviations from normal, are presented.

The pathologic varieties of nystagmus, spontaneous or induced, which are of clinical significance as an expression of disease of the central nervous system, the eyes or the ear are described.

The material in this fourteen-page article is concentrated and worth being read in its entirety by all ophthalmologists.

S. R. IRVINE.

DIVERGENCE PARALYSIS ASSOCIATED WITH TUMOR OF THE BRAIN. N. SAVITSKY and M. J. MADONICK, Arch. Neurol. & Psychiat. **55:** 232 (March) 1946.

Divergence paralysis associated with brain tumor is reported in 4 cases. In 2 of these cases the tumor was a cerebellar neoplasm and in 2, an acoustic neuroma. The authors feel that divergence paralysis is more frequently present with tumors of the posterior fossa than is indicated in the literature. They believe that this divergence paralysis is in some way the result of involvement of the divergence center in the brain. The divergence paralysis may be inconstant. It disappeared in 3 of the 4 reported cases after successful removal of the tumor.

S. R. IRVINE.

NEUROFIBROMATOSIS WITH DEFECT IN WALL OF ORBIT: REPORT OF FIVE CASES. W. T. PEYTON and D. R. SIMMONS, Arch. Neurol. & PSYCHIAT. **55:** 248 (March) 1946.

Five cases of neurofibromatosis with defect in the orbital wall are presented, and some of the general features of neurofibromatosis are discussed. The neurosurgeons who present these cases feel that defects in the wall of the orbit, permitting free communication between the cranial cavity and the orbit, are not as rare as might be inferred from the paucity of reports concerning it, for they encountered these 5 cases in a ten year period at the University Hospitals of the University of Minnesota.

The exophthalmos in cases of neurofibromatosis may be due to two factors: a retrobulbar neurofibroma or an associated tumor other than neurofibroma, such as glioma of the optic nerve. However, the chief reason for the exophthalmos in the cases reported was encroachment on the orbit by the intracranial contents. In most of these cases a pulsating type of exophthalmos is present, the pulsations being due to transmitted pulsations of the cerebrum.

S. R. IRVINE.

Ocular Muscles

EXACT MEASUREMENT OF CONVERGENCE AND DIVERGENCE WITH PRISMS. A. HUDELO, Ann. d'ocul. **178:** 148 (April) 1945.

The author deplores the simple notation of convergence or divergence weakness or excess. He points out the disadvantages of the Maddox rod in measuring phorias and pleads for the more general use of prisms in the measurement of convergence and divergence. He explains simply how the prisms should be held. The largest letter on the acuity chart is used for fixation. The convergence and divergence can then be written in exact prism diopters. To ophthalmologists in this country, where the use of prisms is so generally accepted, it seems strange that there might be ophthalmologists who would not know how to measure prism convergence or divergence, either with the Risley prism or with loose prisms.

P. R. MCDONALD.

Operations

DUST-BORNE INFECTION IN OPHTHALMIC SURGERY. M. H. POST, Am. J. Ophth. **29:** 1435 (Nov.) 1946.

Post concludes from his investigations that to prevent infections in an operating room one should observe the following precautions:

Keep covers on all solutions, towels, instruments, and the like, as much as possible.

Substitute an aqueous solution of zephiran chloride, or similar detergent, for the water bath.

Dip all instruments that are actually to enter the eyeball into a suitable sterilizing solution, or boiling water, for at least two and one-half seconds immediately before use.

Install, as soon as practicable, some method for air sterilization in the operating room.

Treat all blankets and sheets with some type of oil solution.

Treat the floor of the operating room with some type of dust-allaying preparation.

Since these investigations started, approximately 600 intraocular operations have been performed; yet only 1 instance of infection has occurred, and in this case the precaution of dipping the instruments immediately before use, through a misunderstanding, was not observed.

W. S. REESE.

Orbit, Eyeball and Accessory Sinuses

DETERMINATION OF OCULAR TENSION AND RIGIDITY IN RABBITS. E. SCHMERL and B. STEINBERG, Am. J. Ophth. **29:** 1400 (Nov.) 1946.

Schmerl and Steinberg made tonometric determinations of the impressibility of the wall of eyes of rabbits over a prolonged period. The tension and the rigidity were then deduced. Determinations were made at different periods of the day, after instillation of paredrine hydrobromide (para-hydroxy-α-methylphenylethylamine hydrobromide), atropine and pilocarpine and after ingestion of isotonic, hypotonic and hypertonic solutions of sodium chloride. Average values, standard deviations and significant differences were determined.

W. S. REESE.

PROGRESSIVE EXOPHTHALMOS. M. T. BARDRAM, Acta ophth. **22:** 1, 1944.

The literature dealing with malignant exophthalmos is surveyed. Three additional cases are reported, in each of which there was an increased output of gonadotropic hormone in the urine. In 1 case the basal metabolic rate was elevated, although there were no other signs of thyrotoxicosis. The pathogenesis is discussed, the author concluding that the disease is caused by a disturbance in hormone correlation arising after removal of the thyroid gland.

O. P. PERKINS.

Pharmacology

ALKALINE EYE DROPS AND THEIR STABILITY. C. J. BLOK, Ophthalmologica **108**: 217 (Oct.-Nov.) 1944.

The author discusses the advantages of alkaline solutions of drugs to be used in the eye. Because of better penetration, such medicaments are active at lower concentrations of the active ingredients. Alkaline solutions of pilocarpine hydrochloride are stable for about six weeks and solutions of homatropine hydrobromide for about three weeks. With solutions of scopolamine hydrobromide the addition of a mannite solution allows an economy of the alkaloid, owing to better absorption. As a preservative, the addition of 0.03 per cent "nipasol" (a para-hydroxybenzoate) or 1 drop of chloroform per 10 cc. is recommended.

F. H. ADLER.

Retina and Optic Nerve

THE EFFECTS OF ATABRINE [QUINACRINE] ON THE HUMAN VISUAL SYSTEM. L. R. DAME, Am. J. Ophth. **29**: 1432 (Nov.) 1946.

Dame concludes from his investigation that although scotomas and enlargement of the blindspots accompanied suddenly attained high atabrine levels of quinacrine (atabrine) in the blood they disappeared with the lowering of these levels.

W. S. REESE.

ACUTE SPONTANEOUS AND POSTOPERATIVE HYPOTONY IN RETINAL DETACHMENT. I. PORSAA, Acta ophth. **20**: 379, 1942.

The author describes the acute hypotony occurring in cases of retinal detachment; he points out that the condition is the same as that observed as a postoperative complication following diathermy procedures and that a perforating injury of the eyeball may produce an exactly similar clinical picture. He suggests that the hypotony may be due to a concomitant lesion of the choroid, resulting in free passage of fluid from the vitreous through retinal and choroidal ruptures to the suprachoroidal space. This would explain the diminished tension and the increased depth of the anterior chamber, while hemorrhage from the choroidal lesion would explain the greenish discoloration of the iris, the opacities in the vitreous and the cloudiness of the aqueous. Detachment of the ciliary body might account for the pain and irritation that sometimes occur.

O. P. PERKINS.

TREATMENT OF THROMBOSIS OF THE VEINS OF THE RETINA WITH HEPARIN. K. G. PLOMAN, Acta ophth. **21**: 190, 1944.

Thirty-eight patients with thrombosis of the central vein and 31 patients with branch thrombosis were treated with heparin and followed up for an adequate period, i. e., an average of about two years.

The percentage of patients with good final vision was slightly higher than that for an untreated group of patients reported by Odquist. The author warns that treatment is of no use in cases in which increased tension has occurred or in which the papilla is wholly obliterated by massive hemorrhages extending far out toward the periphery and concealing the macular region.

O. P. PERKINS.

Tumors

MALHERBE'S EPITHELIOMA: REPORT OF A RARE CASE. P. S. BORROTO, Rev. Col. med. de Cienfuegos **1**: 1 (Nov.-Dec.) 1945.

The case is presented of an 11 year old child, showing a neoformation of the lower lid, the size of a bean, slightly movable, painless, yellow and without any relation to the malar bone or the upper jaw. The differential diagnosis is analyzed. Microscopic examination of a biopsy specimen revealed a calcified Malherbe epithelioma. This is a rare neoplasm of benign prognosis, with a tendency to recurrence, but it never metastasizes.

M. E. ALVARO.

PRIMARY SYPHILOMA OF THE LIDS. B. P. SANTOS, Soc. de oftal. de São Paulo, May 14, 1945.

The condition was diagnosed as primary syphiloma (protosyphiloma) of the lid. There were pronounced edema of the lids and bulbar conjunctiva and slight reaction of the preauricular glands. The submaxillary and cervical glands were swollen. The Wassermann reaction was positive. The differential diagnosis of sporotrichosis, tuberculosis and a possible neoplasm is made. The appearance, characteristic hardening, glandular reaction, positive Wassermann reaction and regression of the process under treatment all point to the diagnosis of primary syphiloma of the lids.

M. E. ALVARO.

Uvea

POSTERIOR UVEITIS IN A CASE OF SARCOIDOSIS. F. R. NEUBERT, Brit. J. Ophth. **30**: 724 (Dec.) 1946.

A man aged 24 gave a history of radical mastoidectomy at the age of 2 and of malaria at the age of 7 years. Both fundi showed coarse, disseminated choroidal scarring, with some fresh patches of choroidal exudate. The biomicroscope revealed interstitial scarring and opacities in the vitreous. At the age of 29 miliary tuberculosis of the lungs was present. Abdominal symptoms developed, and operation revealed constrictions of the cecum with a well marked "string sign," typical of regional ileitis. The cecum was resected, and microscopic examination of a section showed a picture typical of sarcoidosis.

W. ZENTMAYER.

ANATOMICOCLINICAL STUDY OF CERTAIN FORMS OF BESNIER-BOECK-SCHAUMANN DISEASE. J. FERRIÉ and J. GRYNFELTT, Ophthalmologica **112**: 193 (Oct.-Nov.) 1946.

The authors describe a number of cases which belong to the general class of Mikulicz' disease and cases of Heerfordt's syndrome (uveoparotid fever) in which the anatomic and clinical examination suggested the possibility of grouping these cases together under a common heading. They believe that all the diseases have a common tuberculous basis. There is no bacteriologic confirmation of this, and the authors rely for this opinion on the history, the appearance of the lesions, the histologic picture, the reactions to tuberculin and the influence of

tuberculin therapy on the course of the disease. They believe that the disease complex which they have described is due to an atypical tuberculosis.

F. H. ADLER.

REEXAMINATION OF CENTRAL RUPTURES OF THE CHOROID. E. GODTFREDSEN, Acta ophth. **20:** 337, 1942.

Twelve patients with central rupture of the choroid were reexamined after varying intervals, the average period being three years. Hole formation in the retina occurred once only; nevertheless, the visual acuity of more than one-half the patients became bad because of retinal changes secondary to subretinal and retinal hemorrhages, or to Berlin's edema.

On the other hand, a choroidal rupture right through the fovea does not necessarily mean that the prognosis is bad. Two patients with such a rupture recovered a visual acuity of 6/6; another, an acuity of 6/12.

If improvement of central vision is to occur, it usually does so in the first few weeks after the accident. No improvement occurs after two months.

O. P. PERKINS.

Vision

ILLUMINATION STANDARDS. M. A. TINKER, Am. J. Pub. Health **36:** 963 (Sept.) 1946.

Tinker points out that codes of lighting have been issued by the Illumination Engineering Society either alone or jointly with the American Institute of Architects. He thinks that a more satisfactory approach to hygienic lighting may be achieved by coordinating the work of engineers, physiologists and psychologists. It is obvious that visual work should not be done at critical levels of illumination. There should be an adequate margin of safety to provide for individual variation. For such visual tasks as reading good-sized print (10 to 11 point) on a good quality paper, 10 to 15 foot candles should provide hygienic conditions for normal eyes. For the reading of newsprint, 15 to 20 foot candles should be adequate. In situations involving the reading of handwriting and other comparable tasks, an intensity of 20 to 30 foot candles seems desirable. For tasks comparable to discrimination of 6 point type there should be an intensity of 30 to 40 foot candles. For the most exacting tasks encountered in workday situations 40 to 50 foot candles will be found adequate. There is no valid experimental work now available which indicates a need for an intensity of illumination over 50 foot candles for adequate visual discrimination. These suggestions hold for school children as well as for adults. Intensity of illumination cannot be prescribed without coordinating it with other factors, such as distribution of light and brightness contrast.

J. A. M. A. (W. ZENTMAYER).

VISUAL HALLUCINATIONS AND THEIR RELATIONSHIP TO OPHTHALMOLOGY. JEAN LHERMITTE, Ann. d'ocul. **178:** 129 (April) 1945.

The author states that there are few problems that have aroused as much discussion and about which so much has been written as the subject of hallucinations. He accepts the definition of Ball that a

hallucination is "perception without an object" and distinguishes between an illusion and a hallucination.

Hallucinations may be concerned with the perception of elementary colors, flames or fires or with more complex objects, such as persons, animals and figures. One should note whether the perceived object is moving or fixed, colored or not, bidimensional or tridimensional, transparent or opaque; whether it follows the movement of the eyes; whether it is deviated by a prism, suppressed by closing the eyes or accompanied with a change in the visual field.

The paper contains a general discussion of the visual pathways, with special reference to subjective disturbances brought about by lesions at the various levels. The author concludes that visual hallucinations are not merely manifestations of a general cerebral disturbance. He believes that careful evaluation of the nature of the hallucinations enables one to localize the lesion fairly precisely in the visual system, i. e., in the retina, the tracts or the cortex.

P. R. McDONALD.

Therapeutics

PURE PENICILLIN IN OPHTHALMOLOGY. ARNOLD SORSBY and JOSEPH UNGAR, Brit. M. J. **2**: 273 (Nov. 16) 1946.

In their investigations, Sorsby and Ungar followed the general trend of ocular penicillin therapy of using high concentrations of the drug applied topically and massive doses given parenterally, as first suggested by Struble and Bellows. A pure preparation with the potency of 1,660 units per milligram permitted the authors to increase the tolerated dose above that commonly applied in local therapy. They selected the instillation of ointments containing 25,000 to 100,000 units per gram (about fifty times the usual dose) and subconjunctival injections of 25,000 to 50,000 units (about ten times the usual dose). With regard to iontophoresis, the authors referred to the study of Hamilton-Paterson, who raised basic objections against penicillin ionization. It seems timely to point out that the theoretic assumption of Hamilton-Paterson had been proved in great part unsound and that his conclusions were not applicable to corneal iontophoresis.

The experiments on tolerance of ocular tissues to penicillin confirmed the opinion that most of the irritation caused by the drug was due to the presence of impurities. However, this does not fully answer the question of penicillin toxicity, as it was shown recently that the various isolated species of pure penicillin are injurious to the eye in varying degrees. No conclusions can be drawn from the results of Sorsby and Ungar achieved with intraocular injections of penicillin, as the number of observations was too small and histologic examination was not made.

The observations in the study on penetration and distribution of the drug were generally in agreement with those of other workers if the difference in dose is considered. With the ointments and solutions of the aforementioned strength, satisfactory levels of the drug were obtained in the aqueous, whereas in the vitreous only moderate amounts were present. After subconjunctival injection penicillin was absorbed into the blood. No explanation was given for the fact that the penicillin content in the aqueous of the second, untreated, eye reached in

1 instance 4 units per cubic centimeter, whereas the blood levels did not exceed 2 units per cubic centimeter. A solution of epinephrine hydrochloride (1:1,000) added in equal parts to the penicillin fluid in the subconjunctival injection secured higher and better sustained levels in the aqueous. It was not investigated whether the low p_H of a solution of epinephrine chloride (1:1,000) inactivated any part of the penicillin.

Ointments and subconjunctival injections were employed in the treatment of experimental intraocular infections, mostly produced by a strain of Staphylococcus aureus. Infections of the anterior chamber benefited greatly from these therapeutic procedures, as they do from other local treatment. A progressive suppurative process was observed by the authors in 5 control eyes. This observation is in contrast to the unpredictable course of the inflammation after inoculation of the anterior chamber with various strains of pathogenic Staph. aureus described in the literature. Ten eyes with staphylococcic infection of the vitreous responded surprisingly well to repeated subconjunctival injections of strong solutions of penicillin. The results cannot be compared with those from other laboratories for several reasons: The susceptibility of the infecting organisms for penicillin was not mentioned, and no histologic examination was reported. The interval between the infection and the first treatment was reduced to two hours, a technic unlike that used in similar studies, in which there was an interval of eight hours or more betwen inoculation and penicillin therapy. The early treatment of course favored greatly therapeutic success.

Massive systemic administration of commercial penicillin did not give unusual results. Results of intramuscular injections of penicillin with epinephrine or hexamine or in beeswax corroborated the maintenance of adequate blood levels over a prolonged period as mentioned in previous work on this subject. The therapeutic effects of the systemic therapy were not clear, and can hardly be evaluated without histologic reports on the eyes.

In their discussion of the experimental part, the authors stressed the superiority of subconjunctival treatment of infections of the anterior segment of the eyeball and of the vitreous. Two injections of 20,000 to 25,000 units daily for three days were recommended. It is self evident that the results obtained in the experimental animals cannot be applied directly to man. This view appeared justified in consideration of the unsuccessful results of treatment in 6 of 8 patients with postoperative infections and in 3 patients with infections of the vitreous and intraocular foreign bodies. The optimism of the authors with regard to the effectiveness of the recommended method in treatment of severe postoperative infections of the anterior segment, and especially of the vitreous, in human eyes can therefore hardly be shared. Subconjunctival injections introduce a factor of considerable uncertainty, since it cannot be predicted in the individual case whether enough penicillin will permeate the coats of the human globe and diffuse rapidly enough in the vitreous to stop the infection in the initial stage.

L. VON SALLMANN.

Correspondence

CORNEAL AND CONJUNCTIVAL PIGMENTATION AMONG WORKERS IN HYDROQUINONE

To the Editors:—In connection with Dr. Banks Anderson's article, entitled "Corneal and Conjunctival Pigmentation Among Workers Engaged in the Manufacture of Hydroquinone," which appears in this issue of the ARCHIVES, it may be of interest to note our unsuccessful attempts in the Howe Laboratory to produce pigmentation of the cornea and conjunctiva in rabbits and guinea pigs by acute exposure to parabenzoquinone vapor. This is the compound presumably responsible for the pigmentation in human beings. Three albino rabbits and 6 guinea pigs were introduced into an exposure chamber containing solid quinone spread out on a tray, but separated from contact with the animals. The concentrations of parabenzoquinone vapor in the chamber at various times were as low as 2 parts, and as high as 13 parts, per million. The concentration in the plants where Anderson's patients worked varied between 0.01 and 3.2 p.p.m.[1]

The animals were examined after exposures of four to five days and fifteen days. By the twenty-first day all the animals were dead.

On the fourth day, the corneas showed punctate stippling of the surface, just visible with the low power of the biomicroscope, and punctate "take" with the fluorescein stain. This was similar to, but somewhat more pronounced than, that seen frequently in apparently normal rabbits and guinea pigs. There was no discoloration of the cornea, conjunctiva or nictitating membrane. The white fur of the animals, especially of the nose, feet and abdomen, was colored brown, but the drinking water was also colored brown and may have colored the fur by contact.

By the fifteenth day, 1 of the rabbits and 4 of the guinea pigs were dead. The eyes of the survivors showed somewhat more pronounced stippling and greater staining of the corneas with fluorescein, especially in the palpebral zone but still showed no discoloration. The surviving rabbit and 1 of the surviving guinea pigs which had shown considerable corneal stippling was killed for histopathologic study. The specimens showed only mild keratosis of the corneal epithelium.

DAVID G. COGAN, M.D., and W. MORTON GRANT, M.D., Boston.

Howe Laboratory of Ophthalmology, 243 Charles Street.

1. Oglesby, F. L.; Sterner, J. H., and Anderson, B.: Quinone Vapors and Their Harmful Effects: II. Plant Exposures Associated with Eye Injuries, J. Indust. Hyg. & Toxicol. **29**:74-84, 1947.

News and Notes

EDITED BY DR. W. L. BENEDICT

GENERAL NEWS

Scholarships Granted by Eye Bank for Sight Restoration.—The Eye Bank for Sight Restoration announces the bestowal of two scholarships. Dr. Thomas Duane will investigate the metabolism of the cornea under various conditions of storage at the Howe Laboratory of the Harvard Medical School, and Dr. David Freeman will work at the Yale University School of Medicine on an experiment in tissue transplantation.

Department of Roentgen Therapy, Institute of Ophthalmology, Presbyterian Hospital.—The Institute of Ophthalmology of the Presbyterian Hospital, New York, has recently opened a department devoted to the treatment of ocular diseases and neoplasms with irradiation. The present equipment consists of a high voltage machine, of 220 kilovolts, for the treatment of deeply seated lesions; a low voltage machine, of 120 kilovolts, for more superficial therapy, and a machine of still lower voltage, ranging from 8 to 25 kilovolts, for still more superficial treatment.

Back Copies of Transactions of the American Ophthalmological Society.—Back copies of volumes of the *Transactions of the American Ophthalmological Society*, from the founding of that society through 1939, are available, with the following exceptions:

Volumes I; IV, part 3; VIII, part 2; XVI; XXXIII; XXXIV, and XXXV. Volumes I through XV, XXI and XXVI are unbound and can be procured at $3 each. The other volumes are in standard green binding and can be purchased at $5 each. Orders or requests for information should be addressed to Dr. Maynard Wheeler, 30 West Fifty-Ninth Street, New York 19.

UNIVERSITY NEWS

Postgraduate Course in Ophthalmology, University of California Medical School.—The faculty of the University of California Medical School announces a postgraduate course in ophthalmology for qualified physicians, Sept. 6 to 10, 1948, to be given at the University of California Medical Center, San Francisco, under the sponsorship of the University Extension (Medical Extension), University of California. Complete program and details will be mailed on request to Dr. Stacy R. Mettier, head of postgraduate instruction, Medical Extension, University of California Medical Center, San Francisco 22.

SOCIETY NEWS

Ophthalmological Society of Australia.—The eighth annual meeting of the Ophthalmological Society of Australia will be held at Perth, Western Australia, on Aug. 15 to 21, 1948, in conjunction with the meeting of the sixth congress of the British Medical Association in Australia. The president of the Section on Ophthalmology of the latter is Dr. J. Bruce Hamilton, 174 Macquarie, Hobart, Tasmania; and Dr. John L. Day, St. George's Terrace, Perth, West Australia, is the honorary secretary.

Book Reviews

Principles of the Contact Lens. By H. Treissman, M.B., B.S., F.R.C.S. (Eng.), D.O.M.S., and E. A. Plaice. Price, 10s 6d. Pp. 88, with 40 illustrations. London: Henry Kimpton, 1946.

The authors state that "so far as we are aware, no publication has yet appeared in this country which deals with the principles and uses of these lenses." This book must therefore have preceded by a short time the excellent work "An Introduction to the Prescribing and Fitting of Contact Lenses," by Frank Dickinson and K. G. Clifford Hall, London, Hammond, Hammond & Co., 1946.

This little book is 5/16 inch thick, of which about half is accounted for by the cover. The subjects discussed, which include a description of contact lenses, comparison with spectacles, indications for uses and tolerance, have all been treated in numerous books, articles and papers. The reviewer can think of no reason for publishing this paper as a book, or for its price—more than $2 at the current rate of exchange.

G. M. Bruce.

Klinische und erbbiologische Untersuchungen über die Heredoataxien. By Torsten Sjögren. Acta psychiatrica et neurologica, supplement XXVII. Pp. 200. Copenhagen: Ejnar Munksgaard, 1943.

The unique material of 188 cases of heredoataxias from 118 families was used for the genetic analysis of this disease group. The painstaking mathematical evaluation referring to 3,111 members of the affected families is based on the excellent analysis of the clinical conditions. Of the five groups into which the material is divided, group I (Friedreich's spinal ataxia [hereditary sclerosis, spinal form]) and group III (Marie's cerebellar ataxia [cerebellar hereditary sclerosis]) show the most uniform symptomatology and course of the disease. Group IV contains congenital mild fragmentary forms (*forme fruste*), which do not show any particular tendency to progression. In group I-A and group II less well defined atypical and mixed forms are described.

Prolonged observation over several decades enabled the author to draw definite conclusions about the course of heredoataxias. Progressive mental deterioration, both in Friedreich's spinal ataxia and in Marie's cerebellar ataxia, is noteworthy in the terminal state. Pronounced muscular atrophies were found to be a regular occurrence late in the course of both forms. The early onset of Friedreich's ataxia, at the age of 13 ± 0.7 years, and the late onset of Marie's ataxia, at the age of 34 ± 1.9 years, confirm previous evaluations. The uniformity of the clinical symptoms in various members of the same family was remarkable.

The most important data and conclusions are given in the genetic analysis. After a discussion of the problems involved and the theoretic possibilities, it is calculated that Friedreich's ataxia is probably a recessive monohybrid, whereas Marie's ataxia must be considered a

dominant monohybrid. It can be assumed that the two diseases are different biologic types with reference to their genetic pattern. The occurrence of the two types in the same family was never observed. Particular attention was paid to the distribution of the conditions in the population of Sweden, and the heterozygotes were found to be living in certain distinct areas of the country.

The data of this investigation are lucidly elaborated in tables, and the genetic calculations are presented in a precise way. The material will be valuable in further studies of this important field of clinical neurology.

ERNST HERZ.

Researches on Normal and Defective Colour Vision. By W. D. Wright, Imperial College of Science & Technology, London. Price, $10. Pp. 376, and index. St. Louis: C. V. Mosby Co., 1947.

This excellent volume contains some of the most important publications on color vision of the past two decades. While it does not solve the fundamental problems of color vision—indeed, it probably poses more problems than it solves—it goes far toward furnishing a more advanced view of problems of color vision and a basis for evaluating theories, old or new, which purport to solve them. It is a book which anyone seriously investigating problems of color vision must read.

The book consists largely of collected and rewritten papers reporting the work done since 1926 under grants from the British Medical Research Council. The eight parts of the book consist of an introduction and a description of colorimetric equipment; five important sections on luminosity, color mixture, discrimination, adaptation and defective color vision, and a terminal discussion of the fundamental response curves.

While most of the material has previously been published in article or monograph form by Wright or one of his co-workers, there is a great advantage in having it brought together, correlated, amended and presented in a sequential form. Each part of the book is preceded by a short statement of the problems and a bibliography for further reading.

The redetermination of the mixture curves of the spectrum seemed at the time one of the most important researches which would lead to international standardization of illuminants and color specification, and Wright has been given great credit for this work. Of his later work, the investigations on adaptation, binocular matching, retinal pigmentation and foveal color vision promise great assistance to those whose field is the intricate process of retinal physiology. The inclusion of Pitt's work on dichromatism is a valuable and clarifying portion of the discussion of defective color vision. In particular, the localization of the isopunctal areas for protanopic, deuteranopic and tritanopic subjects on the ICI diagram is of immense assistance to laboratory students who are using pigment stimuli in the study of defective color vision, as well as of color aptitude.

If one could ask for more from this book, it would be the inclusion of actual data instead of curves. For those who wish or need to make transformation on the ICI diagram, the availability of the basic (or transformed) Wright data would frequently be useful.

"Researches on Normal and Defective Colour Vision" is unhesitatingly recommended for reading by all students of color vision physiology.

LEGRAND H. HARDY.

Ophthalmic Literature. Sir Stewart Duke-Elder, Editor. Vol. I, No. 1. Pp. 104. Issued quarterly. London, England: British Journal of Ophthalmology, Limited.

A new abstract journal has appeared in English under the title *Ophthalmic Literature* and is sponsored by the *British Journal of Ophthalmology*. It will work in association with the abstracting service of the British Medical Association for general medical literature, and abstracts will be exchanged with *Ophthalmologica Ibero Americana*. In addition to the abstracts from ophthalmic journals, it will bring articles with ophthalmic bearing to be found in journals on general medicine, surgery and pathology, as well as in the more purely scientific periodicals on optics, physics, physiology and biochemistry. In addition, general review articles on important subjects will appear from time to time.

This new journal will appear quarterly, with the year running from June to June, the abstracts beginning with articles published from Jan. 1, 1947, and there will be a cumulative annual index.

The editor is Sir Stewart Duke-Elder, and the editorial board includes A. G. Gross, A. J. B. Goldsmith, A. G. Leigh, Arthur Lister, A. Seymour Phipps and Katherine Tansley.

To the reviewer, the requisites of an abstract journal consist in the proper selection of articles from ophthalmology and from its neighboring departments, and in the availability of the abstracters, who not only must be conversant with the subject but must be able to pick out the salient features of the article in question. This takes time and requires ability and industry.

The contents of the first number show that these conditions have all been met. The field has been well covered; the task of the abstracter is well done, and the subject of the review article, which in this issue is "Penicillin in Ophthalmology," is admirably covered.

Congratulations are offered to the editor and to his board on the appearance of their first number, with every good wish for the future success of this laborious and courageous undertaking.

ARNOLD KNAPP.

May's Manual of Diseases of the Eye. Edited by Dr. Charles A. Perera. Nineteenth edition. Price, $4. Pp. 521, with 387 illustrations, some in color. Baltimore: Williams & Wilkins Company, 1947.

This new edition has been thoroughly revised and brought up to date. It is stated in the preface that the additions consist in penicillin therapy, the modern theory of color vision and its anomalies, thyrotropic and thyrotoxic exophthalmos, congenital cataract following maternal rubella and ocular brucellosis.

Dr. May's popular textbook is kept up to date by the energy of its present editor, Dr. Charles A. Perera, and should continue its popularity and serve as a reliable and practical introduction to the practice of ophthalmology. Though a number of illustrations have been replaced, most of the remaining black and white illustrations have outlived their distinctness, and the presswork is poor.

ARNOLD KNAPP.

Physiologie oculaire clinique. By A. Magitot. Price, 750 francs. Pp. 458, with 235 illustrations. Masson & Cie, Paris, 1946.

The author has been interested for the last quarter of a century in ocular physiology, particularly in the field of ocular tension and in the retina and iris. He retired in 1940 from active duty in the Lariboisière Hospital, of Paris, where he had succeeded Victor Morax and Poulard, and was able to devote the next four or five years to collecting his papers and writing this excellent book. There was a distinct need for it, since no similar textbook was available in French except Nicati's, which is both out of print and out of date.

This book is written by and for the practicing ophthalmologist, and physiology is approached with a constant view to the explanation of clinical facts. Reversely, clinical facts are used to support and enlighten physiologic theories. If the book had been written by a "pure" physiologist, and not by a practicing ophthalmologist interested in physiology, it would probably have been slightly different. As it is, it makes excellent reading and is a most useful textbook for reference.

The first few chapters are devoted to the lids, ocular sensitivity and the autonomic nervous system of the eye. Next comes the most personal part of the book, for most of the author's previous publications had dealt with the nutrition of the eye, the intraocular fluids and ocular tension. Anyone familiar with these previous papers can readily guess that little importance is given to filtration and to the pathology of the angle in the regulation and anomalies of ocular tension. Although many may not agree with the author, none can read his views without interest, for they are coherent, clearly stated and supported by experimental work and by a complete knowledge of the literature up to the war.

The following chapters deal with the cornea, the iris, the pupil and the lens. They are complete and up-to-date. Then comes a hundred pages on the physiology of the retina, which to the reviewer's mind is probably the best part of the book. This subject is approached in the light of the dual theory (cones for vision in broad daylight, rods for vision in reduced illumination). But even if all readers do not accept this view, they will find all that is known on the retina and its physiology. They can easily transpose this to their own plane of reference.

The book continues with the physiology of the nerve fibers and of the receptor area in the brain. This leads to a study both of the visual field and of the neurologic symptoms related to lesions of the occipital lobe. The last chapters are devoted to ocular muscles and binocular vision.

There are over two hundred illustrations, and numerous references appear at the end of each chapter. Physiologic optics has deliberately been left aside.

EDWARD HARTMANN, M.D.

Ocular Therapeutics. By William J. Harrison. Price, $3.50. Springfield, Ill.: Charles C Thomas, Publisher, 1947.

Dr. Harrison's small textbook aims to be an accessible reference book for ophthalmic prescriptions. It serves the double purpose of giving help in writing prescriptions and of giving the indications for their use. The drugs selected are those that have stood the test of experience and are official in the United States Pharmacopeia, with one exception (paredrine hydrobromide), and are accepted by the Council on Pharmacy and Chemistry.

The reader will find useful information on isotonic solutions, buffer solutions, the application of moist heat and moist cold, astringents, caustics, antiseptics, mydriatics, cycloplegics and miotics. The author still believes in silver nitrate and in mercury bichloride solution but rejects yellow mercuric oxide, boric acid and ichthammol. The treatment of acid burns and alkaline burns is also given. Short chapters on foreign proteins, old tuberculin, vitamins, sulfonamide drugs and penicillin conclude the book. These, in the reviewer's opinion, are too condensed in view of their importance.

Every physician has his favorite remedies with which the desired results are obtained, so that practice is often a personal matter; at the same time, the proper administration of the remedy must not be overlooked in testing the efficiency of treatment.

With the author's desire for condensation, a number of omissions have occurred which in the opinion of the reviewer would otherwise enlarge the book's usefulness.

The book is splendidly printed, on excellent paper. Its teaching is sound, and the young specialist will find a reliable guide for this important part in the treatment of ocular diseases.

ARNOLD KNAPP.

Documenta ophthalmologica. Edited by F. P. Fischer, Utrecht, Netherlands; A. J. Schaeffer, Los Angeles, and Arnold Sorsby, London. Pp. 482. Zurich, Switzerland: Documenta Press, 1938.

This new journal is to bring monographs treating questions and problems which have been solved to a certain extent; in other words, it presents an up-to-date treatment of the problems in question and should be a complement to the library of the specialist. In volume 1, printed in 1938, and which is in stock, papers on these subjects appeared: Processes of Adaptation in the Vertebrate Retina in the Light of Recent Photochemical and Electrophysiological Research, R. Granit, Helsingfors, Finland; Der Wasserhaushalt des Auges und seiner Teile, F. P. Fischer, Utrecht, Netherlands; La circulation rétinienne, P. Bailliard, Paris; Die Bedeutung der Carotinoide für die Augen, P. Karrer, Zurich, Switzerland; Le vitamine nei loro rapporti con l'oftalmologia, A. Juhász-Schäffer, Milan, Italy; Symptomatologie du glaucome et le problème pathogénique, A. Magitot, Paris, and Le problème physico-chimique de l'opacification du cristallin, J. Nordmann and P. Reiss, Strasbourg, France.

Volume 2 is in process of production and will be published by Dr. W. Junk, Amsterdam, Netherlands.

ARNOLD KNAPP.

A Hand-Book of Ocular Therapeutics. By the late Sanford R. Gifford, M.D.; revised by Derrick Vail, M.D. Fourth edition. Price, $5. Pp. 336, wtih 66 illustrations. Philadelphia: Lea & Febiger, 1947.

The last edition of Gifford's "Hand-Book of Ocular Therapeutics" appeared in 1942; so a revision is timely. This task, and the incorporation of new material which was made necessary by progress along certain lines, fell to Dr. Derrick Vail, who was assisted by Dr. F. C. Cordes in the revision of the chapter on "Specific and Non-Specific Protein Therapy," on parts of the chapter on "Physical Therapy" and on all of the chapters on "Diseases of the Optic Nerves and Central Visual Pathways." Dr. J. G. Bellows has been helpful in revising and bringing up to date the information on the sulfonamide drugs and the antibiotic substances. It seemed wisest to defer the introduction of the new antihistamine agents until further knowledge is gained. The chapter on "Disorders of the Muscular Apparatus" has been omitted, with perfectly correct reasoning. It is always difficult to decide on the selection of topics for a book on therapeutics, as many are better treated in the regular textbook or in a special volume.

The rest of the book is unchanged, and, with the characteristic style and personality of the lamented author, its excellent qualities are maintained.

Dr. Vail and his associates are to be congratulated on the appearance of the new edition of this book, which will continue to be essential to every practicing ophthalmologist.

ARNOLD KNAPP.

Bulletins et mémoires de la Société française d'ophtalmologie. 1940-1946. Pp. 411. Paris: Masson & Cie, 1946.

The report for this year, entitled "Les aspects pathologiques du fond de l'oeil dans las affections de la rétina (Atlas ophthalmoscopique), was presented before the *Société française d'ophtalmologie* by Gabriel Renard on May 8, 1939, and, as is customary, was published as a separate volume (reviewed in the ARCHIVES **38:** 129 [July] 1947). This report is the thirteenth in this remarkable series of monographs on the ophthalmoscopic examination of the fundus oculi, which has added so much to the renown of the French Ophthalmological Society. This volume of the transactions of the society brings the discussion on this report, which took place on May 21, 1946, at the postponed meeting of the society. The remainder of the meeting was occupied with the presentation of about sixty papers concerned with clinical observations on many subjects and their discussion. Among these papers, attention may be drawn to the following: "Intravenous Injections of Procaine in Treatment of Thrombosis of the Retinal Veins," by Schiff-Wertheimer and Gaillard; "Corneal Grafting," "Cataract," "Glaucoma," "Clinical Proof of Permeability of the Blood-Ocular Barrier to Fluorescein," by Amsler; "Retinal Adaptation," by Jayle and Durgaud, and "Postoperative Complications of Operations for Retinal Detachment," by Schiff-Wertheimer and Frileux.

The society is again in full activity, and it is to be hoped that there will be no further interruption in its yearly meetings.

ARNOLD KNAPP.

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